Normal Bone Marrow

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The bone marrow examination is an important diagnostic procedure used for a wide variety of clinical conditions such as the diagnosis of myeloid or lymphoid neoplasms, various reactive conditions or metastatic, non-hematopoietic malignancies. Bone marrow examination is also used for confirmation or monitoring of a remission state, residual or recurrent disease state, or regeneration of bone marrow after various therapies. Bone marrow aspiration and biopsy of adequate quality are considered to represent overall bone marrow function.

A basic understanding of bone marrow structures and the correct identification of cells comprising normal bone marrow are very important in the interpretation of bone marrow pathology. The bone marrow is a well-organized structure confined in cortical bone and traversed by medullary or trabecular bone. The bone marrow has three components: hematopoietic cells, stroma/microenvironment, and medullary bone. Hematopoietic cells are embedded in a connective tissue stroma in intertrabecular spaces of medullary bone. The bone marrow is almost entirely occupied by hematopoietic cells, with the highest cellularity at birth or early infancy. The hematopoietic cells gradually decrease in the bone marrow with aging, and the bone marrow is replaced by adipose cells (fat cells). Hematopoietic cells derived from multipotent stem cells can be further differentiated into several lineage cells: erythrocytes, granulocytes, monocytes, megakaryocytes, and lymphocytes.

Tables 1.1, 1.2, and 1.3 list the characteristic cytologic features of erythroid cells, granulocytic cells, and megakaryocytic cells. These tables illustrate the various stages of maturation from the earliest recognizable immature cells to mature cells in the bone marrow. Erythroid precursor cells (normoblast or erythroblast) develop adjacent to macrophages and are subdivided into pronormoblasts, basophilic normoblasts, polychromatophilic normoblasts, and orthochromic normoblasts. Immature granulocytic cells develop adjacent to trabecular surfaces or arterioles and are further subdivided into blasts, promyelocytes, myelocytes, metamyelocytes, band neutrophils, and segmented neutrophils. Megakaryocytes, the largest hematopoietic cells in bone marrow, can be easily identified adjacent to sinusoids, but megakaryoblasts or immature megakaryocytes are often difficult to recognize in the bone marrow and can be readily identified in conjunction with immunohistochemistry or immunophenotype.

The marrow stroma is composed of fibroblasts, macrophages, adipose cells, osteoblasts, osteoclasts, sinusoids or capillaries, and endothelial cells.

In this chapter, characteristic cytologic and histologic features of various types of hematopoietic cells (particularly a spectrum of maturing hematopoietic cells) and stromal cells observed in normal bone marrow are described with representative pictures (Figs. 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 1.10, 1.11, 1.12, 1.13, 1.14, 1.15, 1.16, 1.17, 1.18, 1.19, 1.20, 1.21, 1.22, 1.23, 1.24, 1.25, 1.26, 1.27, and 1.28). Bone marrow cells that are morphologically similar and easy to misidentify are illustrated with a comparison of their cytologic features.

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Table 1.1 Maturation of erythroid cells in bone marrow

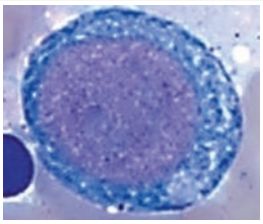
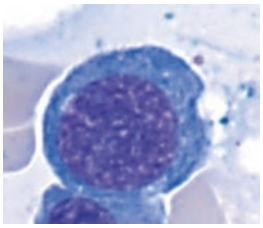
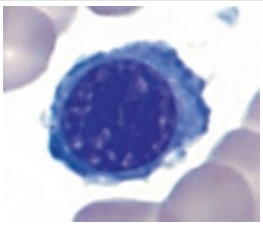
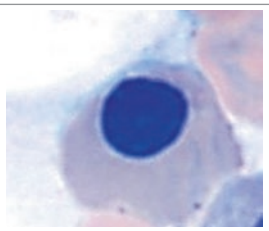
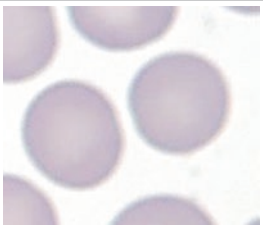
Cell type	Characteristic morphology	Description
Pronormoblast (proerythroblast)		The most immature and largest cells in erythroid lineage (12–24 μm), relatively high nuclear to cytoplasmic (N/C) ratio (7–8:1), round to slightly oval nucleus, finely reticulated chromatin, prominent nucleoli (≥ 1), and agranular basophilic cytoplasm
Basophilic normoblast		Smaller cells (10–17 μm) than pronormoblast, round nucleus, high N/C ratio (6:1), open to slightly condensed chromatin, distinct parachromatin, rarely visible or absent nucleoli in later stage, and deep basophilic cytoplasm
Polychromatophilic normoblast		Smaller cells (10–15 μm) and lower N/C ratio (4:1) than basophilic normoblasts, round nucleus with condensed chromatin, often cartwheel appearance, visible perinuclear halo, no nucleoli, and blue-gray to pink-gray cytoplasm
Orthochromic normoblast		More mature and smaller cells (8–12 μm) than polychromatophilic normoblast, abundant cytoplasm (N/C ratio 1:2) with pink-orange and minimally basophilic color similar to erythrocytes, round nucleus, and densely condensed or pyknotic chromatin
Erythrocyte		The most mature cells (7–8.5 μm), pink-orange to salmon color, and no nucleus

Table 1.2 Maturation of granulocytic cells in the bone marrow

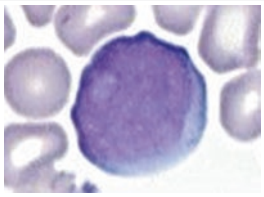
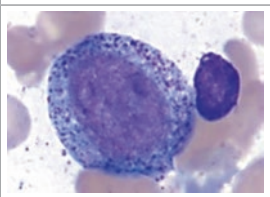
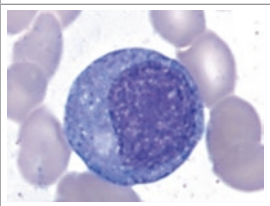
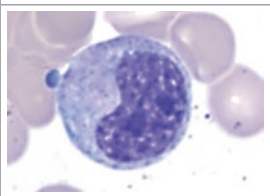
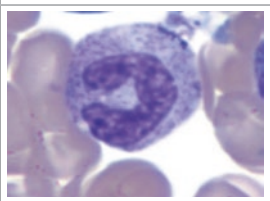
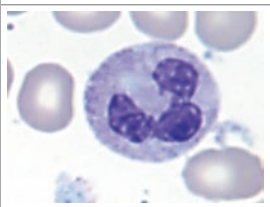
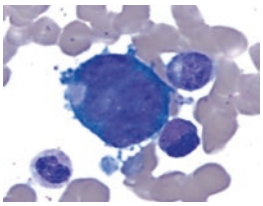
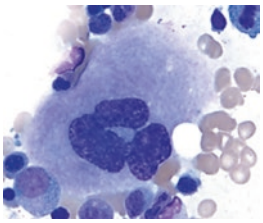
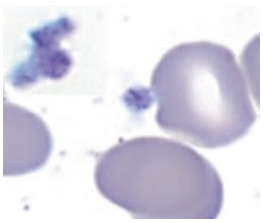
Cell type	Characteristic morphology	Description
Myeloblast		The most immature granulocytic cells (15–20 μm), with high N/C ratio (4–7:1), round to oval nucleus, fine to reticular chromatin with distinct nucleoli (1–5), and moderately basophilic cytoplasm with absent or minimal azurophilic granules
Promyelocyte		Slightly larger cells (14–24 μm) than myeloblasts, with high N/C ratio (3–5:1), eccentric round to oval nucleus, slightly coarse or finely reticular chromatin, distinct nucleoli (1–3), basophilic cytoplasm with paranuclear hof and prominent azurophilic (primary) granules, which may overlie the nucleus
Myelocyte		Slightly smaller cells (10–18 μm) than blasts, with more abundant cytoplasm (N/C ratio 1–2:1), eccentric round to oval nucleus, more condensed chromatin, no nucleoli, bluish to pink cytoplasm with paranuclear hof, abundant lilac (secondary) granules, and scattered few azurophilic (primary) granules
Metamyelocyte		Size similar to or slightly smaller (10–18 μm) than myelocytes, with abundant cytoplasm (N/C ratio 1–1.5:1), indented or kidney-shaped nucleus (indentation less than half the width of the nuclear margin), condensed chromatin, no nucleoli, pinkish cytoplasm with many secondary granules and rare primary granules
Band neutrophil		More mature cells (10–18 μm) similar to metamyelocytes, abundant cytoplasm (N/C ratio 1:1.2–1.5), indented or band-like or sausage-like nucleus (indentation more than half the width of the nuclear margin), condensed chromatin, no nucleoli, and pinkish cytoplasm with abundant secondary granules
Segmented neutrophil		The most mature cells (10–18 μm), with abundant cytoplasm, more condensed nucleus with 3 to 5 distinct lobes connected by thin filaments, and pinkish cytoplasm packed with secondary granules

Table 1.3 Maturation of megakaryocytic cells in the bone marrow

Cell type	Characteristic morphology	Description
Immature megakaryocyte		Smaller cell (size > 20 μm) than mature megakaryocytes, with high N/C ratio, one round lobe, horseshoe-shaped or slightly lobulated nucleus, variably clumped chromatin, and deeply basophilic cytoplasm with cytoplasmic blebbing
Mature megakaryocyte		The largest hematopoietic cells (20–160 μm) with variable size and shape, more abundant pink cytoplasm with abundant azurophilic granules, and highly folded and connected nuclei with multilobation (2–16 lobes) on later stage of maturation, clumped chromatin, and no nucleoli
Platelet		The most mature and smallest (2–4 μm) megakaryocytic cells, with pale to gray-blue cytoplasm, no nucleus, and dispersed purple to red azurophilic granules

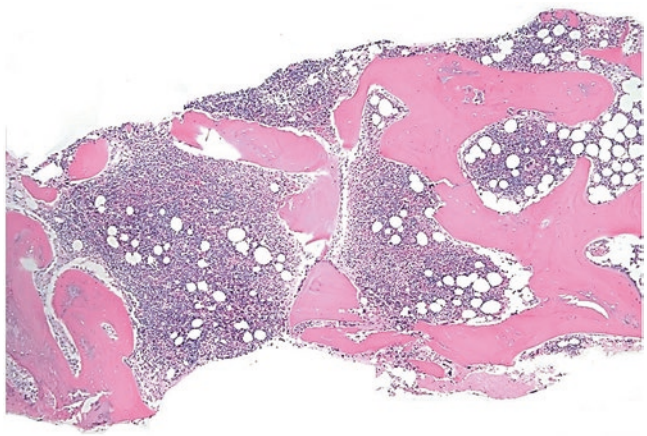


Fig. 1.1 Bone marrow core biopsy from a 4-year-old boy shows a good quality with adequate size, cortical bone, and several intertrabecular spaces with hematopoietic cells and adipose cells. The marrow cellularity is estimated by the percentage of hematopoietic cells in the total volume of marrow space; it declines with age, showing the highest cellularity in an infant or a young child and the lowest in an elderly person. In this slide, the bone marrow space is occupied by approximately 90% cellularity with hematopoietic cells and approximately 10% by adipose cells, which is normal cellularity for the age of 4 years

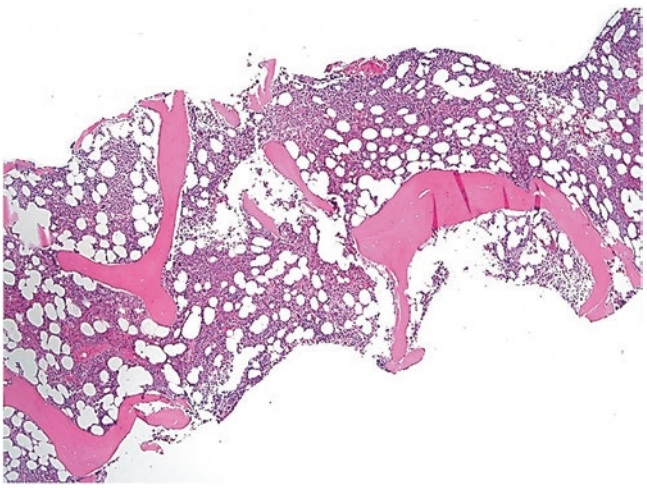


Fig. 1.2 Bone marrow core biopsy from a 42-year-old woman shows that the marrow space is occupied by approximately 50—60% hematopoietic cells with trilineage hematopoiesis and approximately 40—50% adipose cells, which is normal cellularity for the age of 42 years

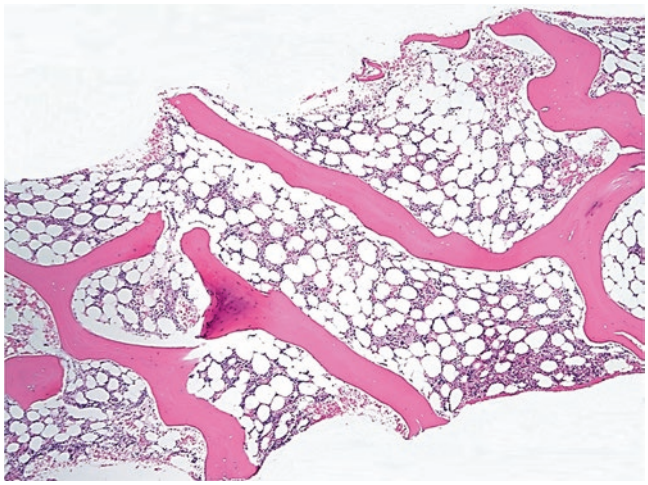


Fig. 1.3 Bone marrow core biopsy from a 78-year-old man shows that the marrow space has significantly reduced hematopoietic cells (approximately 20%), which are replaced by adipose cells (approximately 80%). The cellularity in this figure is normal for the age of 78 years

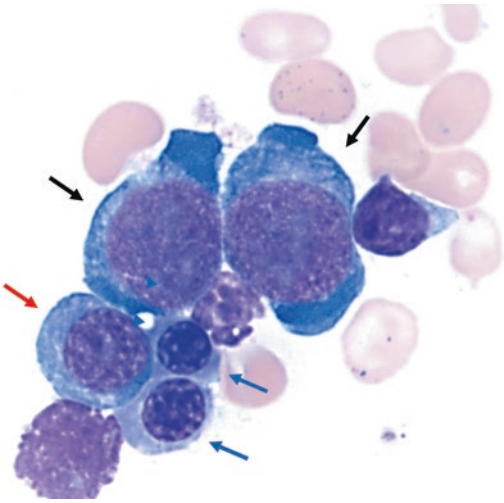


Fig. 1.4 Bone marrow aspirate smear shows various stages of maturation in erythroid precursors. The two largest cells (*black arrow*) are pronormoblasts (or proerythroblasts), the most immature erythroid cells, which are characterized by intensely basophilic cytoplasm, a large nucleus with immature chromatin, and few prominent nucleoli. A basophilic normoblast (*red arrow*), the cell in the next stage of erythroid maturation, is smaller than pronormoblasts but has basophilic cytoplasm owing to abundant RNA, slightly condensed chromatin, and visible nucleoli. Two cells in the bottom (*blue arrow*) are polychromatophilic normoblasts, which can be differentiated from basophilic normoblasts by their smaller size, gray cytoplasmic color related to an accumulation of hemoglobin, significantly condensed chromatin with clumping, and absent nucleoli. A mature lymphocyte is also shown

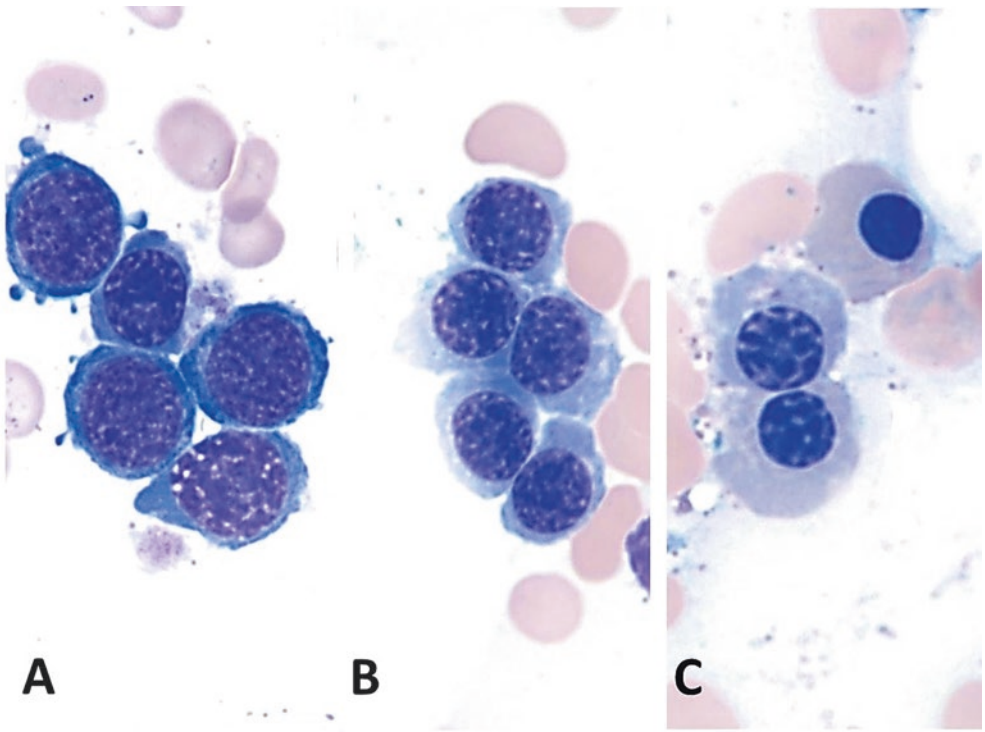


Fig. 1.5 A spectrum of maturing erythroid precursors in bone marrow aspirate smears. (**A**) Basophilic normoblasts. (**B**) Polychromatophilic normoblasts. (**C**) Orthochromic normoblasts. As erythroid precursors mature, a gradual change in cytoplasm from deep blue to gray-blue to pink-orange color, with progressive maturation of nuclear chromatin from less condensed to significantly clumped to very dense and homogeneous chromatin, and a slight reduction in the size of the cells

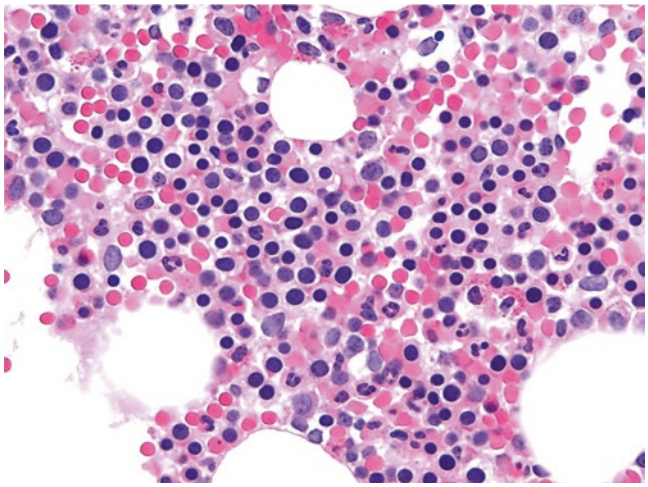


Fig. 1.6 Bone marrow core biopsy shows normal hematopoietic cells with prominent erythroid precursors in the marrow space. Erythroid precursors can be differentiated from other hematopoietic cells by their distinct round nuclear contours and very dense, homogenous nuclear chromatin

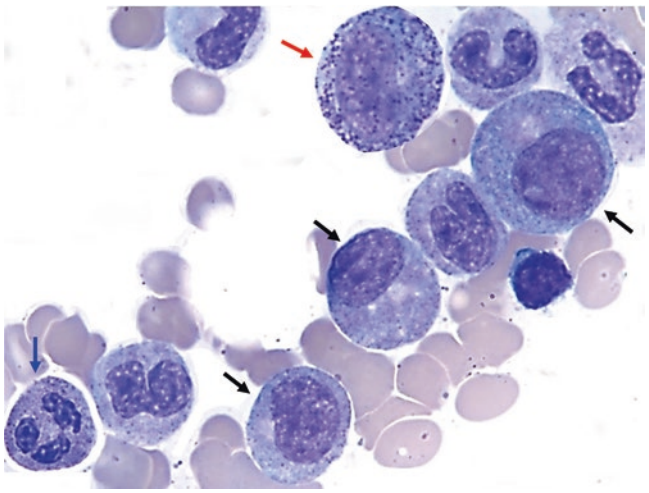


Fig. 1.8 Bone marrow aspirate smear shows various stages of maturing granulocytic cells. One promyelocyte (*red arrow*), three myelocytes (*black arrow*), four band neutrophils (*no arrow*), and one segmented neutrophil (*blue arrow*) are shown. The promyelocyte has basophilic cytoplasm with a paranuclear hof, an eccentric, round to oval nucleus, visible nucleoli, and distinct, prominent, and coarse azurophilic (primary) granules overlying the nucleus and cytoplasm. The myelocytes have a similar or slightly smaller size, a similar eccentric, round to oval nucleus, and a paranuclear hof corresponding to Golgi apparatus, but they have more condensed chromatin and blue to pink cytoplasm with abundant lilac (secondary) granules. Band and segmented neutrophils can be differentiated by the shape of their nucleus and chromatin. The segmented neutrophil has more condensed nuclear chromatin with clumping and nuclear lobes that are connected by thin filaments; the band neutrophils have a band-shaped, sausage-shaped, C-shaped, or U-shaped nucleus

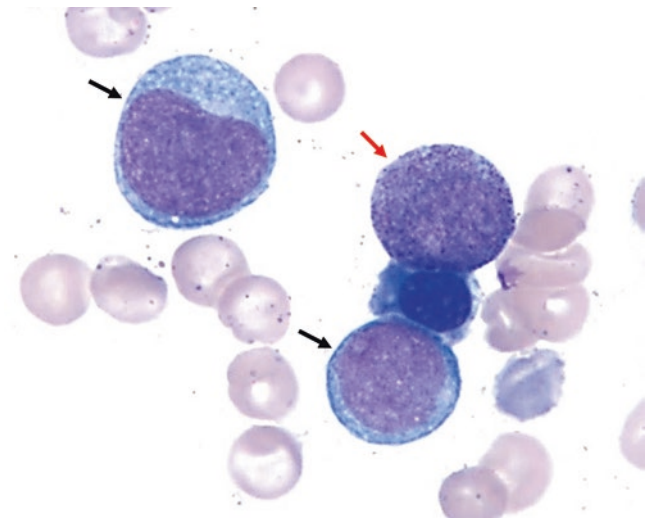


Fig. 1.7 Bone marrow aspirate smear shows two myeloblasts (*black arrow*), one promyelocyte (*red arrow*), and one polychromatophilic normoblast (*no arrow*). Myeloblasts, the most immature granulocytic cells, have an intermediate to large size, a high nuclear to cytoplasmic (N/C) ratio, moderate basophilic cytoplasm, a round nucleus, fine, uniform chromatin, and several nucleoli. Promyelocytes can be similar or slightly larger in size than blasts, with a high N/C ratio, a round nucleus with slightly coarse chromatin and visible nucleoli, and basophilic cytoplasm with a paranuclear hof; however, they have prominent azurophilic granules in the cytoplasm and overlying the nucleus, which often obscure the nucleus border

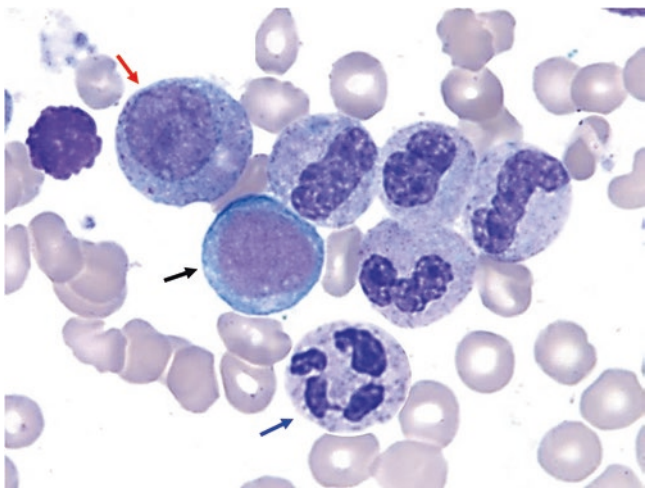


Fig. 1.9 Bone marrow aspirate smear shows a spectrum of maturing granulocytic cells. One myeloblast (*black arrow*), one myelocyte (*red arrow*), four band neutrophils (*no arrow*), and one segmented neutrophil (*blue arrow*) are shown. Band neutrophils often can be difficult to differentiate from segmented neutrophils because their nucleus can be folded or twisted, as shown in this figure. The constricted, thin filaments between nuclear lobes can be seen only in segmented neutrophils

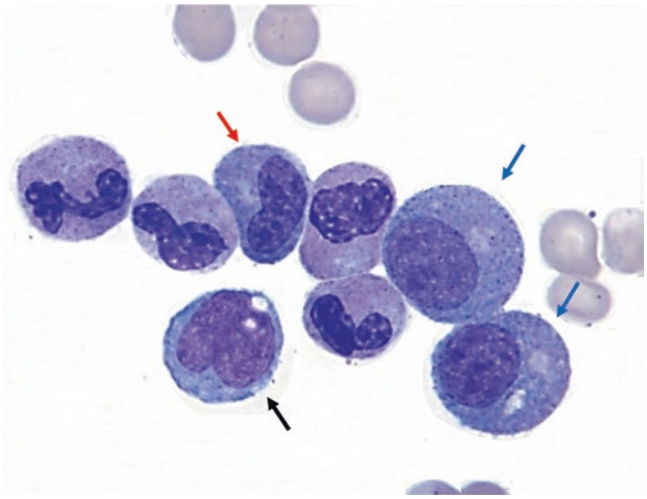


Fig. 1.10 Bone marrow aspirate smear shows various stages of maturing granulocytic cells and one monocyte. Two myelocytes (*blue arrow*), one metamyelocyte (*red arrow*), and four band neutrophils are shown. The metamyelocyte (*red arrow*) can be differentiated from a band neutrophil by its nuclear shape. The nucleus of a metamyelocyte is indented or kidney-shaped and has less indentation (less than half the width of the nucleus) compared with the nucleus of band neutrophils, which has an indentation greater than half of the width of the farthest margin. The monocyte (*black arrow*) is a large cell (10–20 μm) with round to oval shape and abundant gray to gray-blue cytoplasm (N/C ratio 2:1–4:1) with azurophilic granules and/or vacuoles, a round to indented, lobulated, or irregular nucleus, clumped chromatin that is less dense than in neutrophils, and no nucleoli

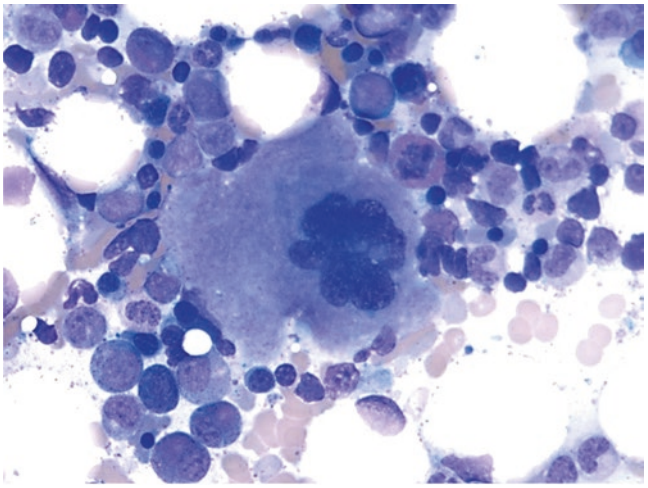


Fig. 1.12 Bone marrow aspirate smear shows a large, mature megakaryocyte, with other hematopoietic cells surrounding the megakaryocyte. As shown here, the megakaryocyte is the largest hematopoietic cell in the marrow and it is pleomorphic; it has abundant pink cytoplasm with numerous azurophilic granules that can produce platelets, and it has clumped nuclei with multiple lobes generated by endomitosis. The multiple nuclear lobes are connected by fine chromatin threads and often are highly folded or overlying other nuclear lobes

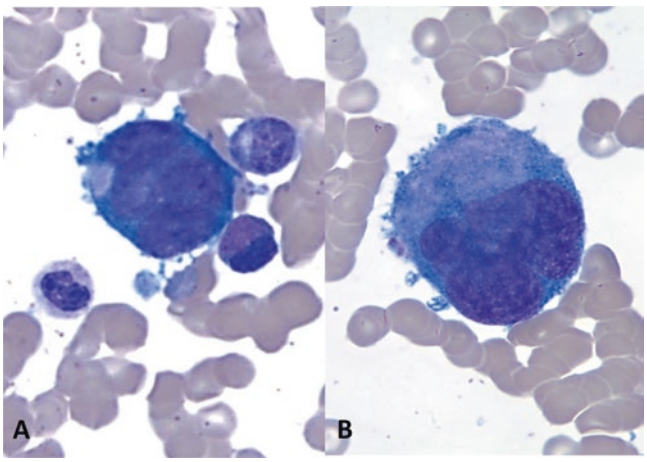


Fig. 1.11 (**A**) and (**B**). Bone marrow aspirate smears show two immature megakaryocytes with larger size than neutrophils, high N/C ratio, deep basophilic cytoplasm, non-lobulated or less-lobulated nucleus, and cytoplasmic blebs. Megakaryocytes in the early, immature stage can have nucleoli. These cells lack cytoplasmic granules, which are seen in mature megakaryocytes

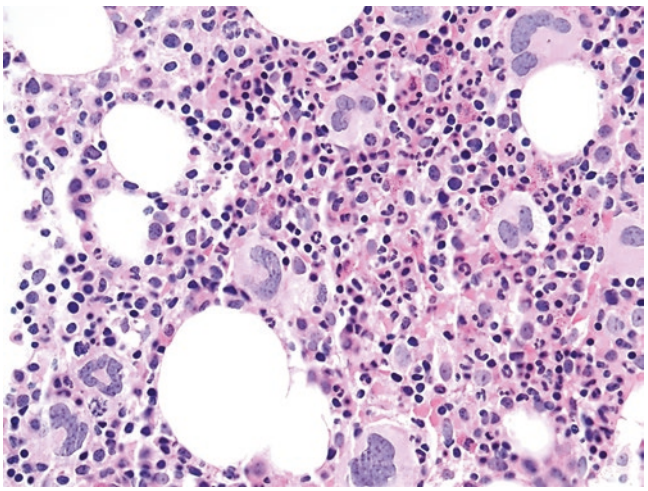


Fig. 1.13 Bone marrow core biopsy shows multiple mature megakaryocytes and other hematopoietic cells. Mature megakaryocytes are very large and pleomorphic, showing variable numbers of nuclear lobes and abundant pink cytoplasm. Megakaryocytes can be readily identified adjacent to sinuses in the marrow

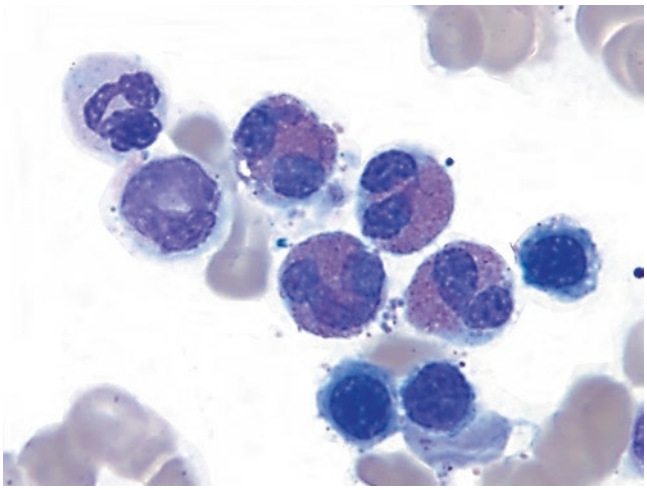


Fig. 1.14 Bone marrow aspirate smear shows four mature eosinophils in the center of the image. Eosinophils (10–17 μm) have abundant cytoplasm with numerous coarse, bright red to orange refractile granules of uniform size, segmented nuclei with two or three lobes connected by thin filaments of chromatin, and coarsely clumped nuclear chromatin

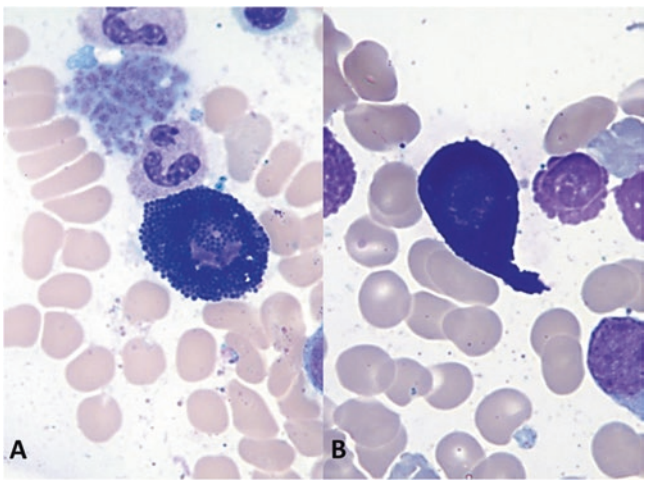


Fig. 1.16 (**A**) and (**B**). Bone marrow aspirate smears illustrate two mast cells. Mast cells (12–30 μm), called *tissue basophils*, are connective tissue cells of hematopoietic origin. Mast cells are round to oval-shaped cells with a single small, round nucleus and abundant cytoplasm packed with numerous coarse, round purple to bluish-dark metachromatic granules overlying and obscuring the border of the nucleus and cytoplasm. Mast cells are approximately twice as large as blood basophils and have more abundant cytoplasm, a round nucleus, and numerous round, uniform basophilic granules obscuring the nucleus and often extending out to the cytoplasm

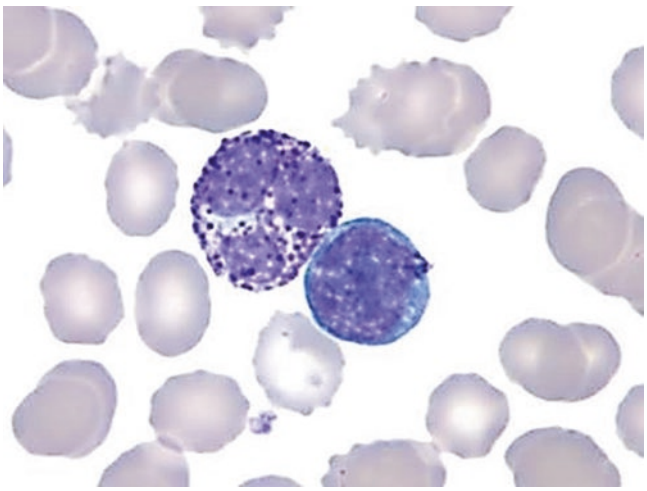


Fig. 1.15 Bone marrow aspirate smear shows a mature basophil (on the left) and a lymphocyte. Basophils (10–15 μm) have abundant cytoplasm with coarse, dense, purple to dark granules, which vary in size and shape, are unevenly distributed in the cytoplasm, overlie the nucleus, and obscure segmented nuclei with two or three lobes. Cells morphologically resembling basophils are segmented neutrophils with toxic granulation or mast cells

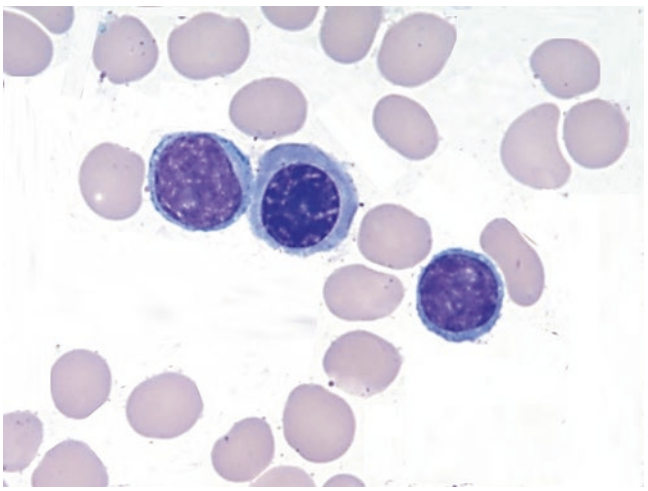


Fig. 1.17 Bone marrow aspirate smear shows two mature lymphocytes, with one polychromatophilic normoblast in the center of the image. Lymphocytes are small cells (7–15 μm) with a single, round, ovoid, or slightly indented nucleus, a scant to moderate amount of cytoplasm (N/C ratio 2:1 to 5:1), pale blue color, and sometimes a perinuclear halo, diffusely dense chromatin, and no visible nucleoli. Some larger lymphocytes may have variable numbers of coarse, azurophilic granules in the cytoplasm

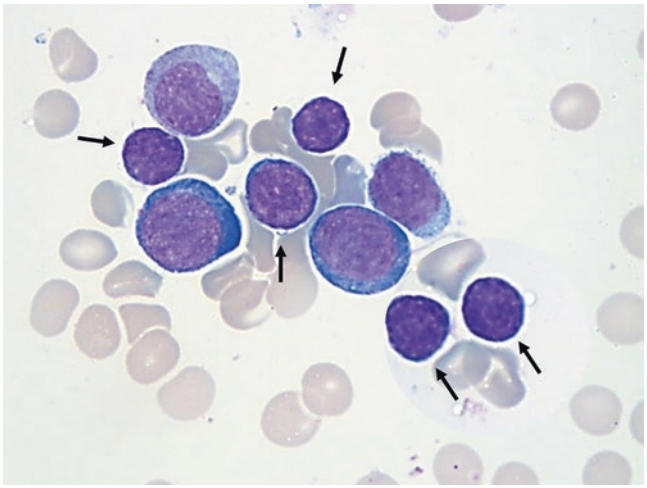


Fig. 1.18 Bone marrow aspirate smear shows five hematogones (*black arrow*) in a young child. Also present are one mature lymphocyte, two basophilic normoblasts, and one myelocyte. Hematogones are small- to intermediate-sized cells with very scant cytoplasm, a round to slightly irregular nucleus, dense homogenous chromatin, and indistinct nucleoli. Hematogones are benign lymphocyte precursors encountered in the bone marrow of an infant or a young child, associated with solid tumors, after aggressive chemotherapy or transplantation, or in an immunosuppressed state. By morphology, hematogones are often difficult to differentiate from lymphoblasts in acute lymphoblastic leukemia. Characteristic immunophenotype as well as certain clinical conditions can help to make a correct identification of hematogones

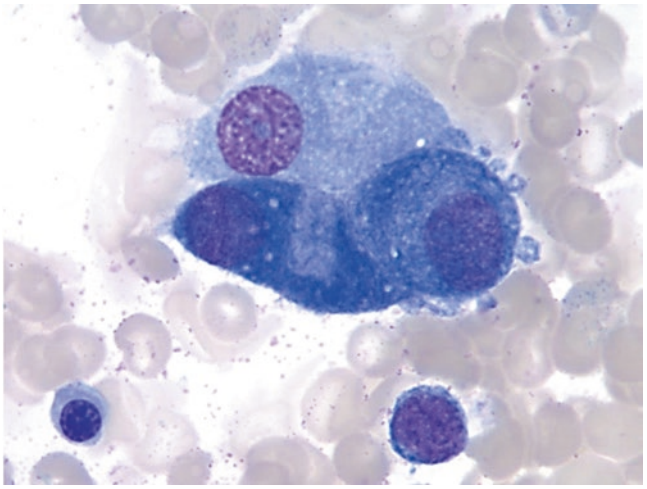


Fig. 1.20 Bone marrow aspirate smear shows a small cluster of osteoblasts. Osteoblasts, bone-forming cells, are large cells (20–50 μm) with an oval, comet, or tadpole shape, abundant deep basophilic cytoplasm with indistinct borders, an eccentrically located or partially extruded, single round to oval nucleus with reticular chromatin, prominent Golgi apparatus, called the *hof*, or pale, staining cytoplasm away from the nucleus, and one or more nucleoli. Osteoblasts can be differentiated from plasma cells by their large size, the prominent hof away from the nucleus, and their often indistinct cytoplasmic borders. Osteoblasts can be seen as small clusters in growing children or adolescents

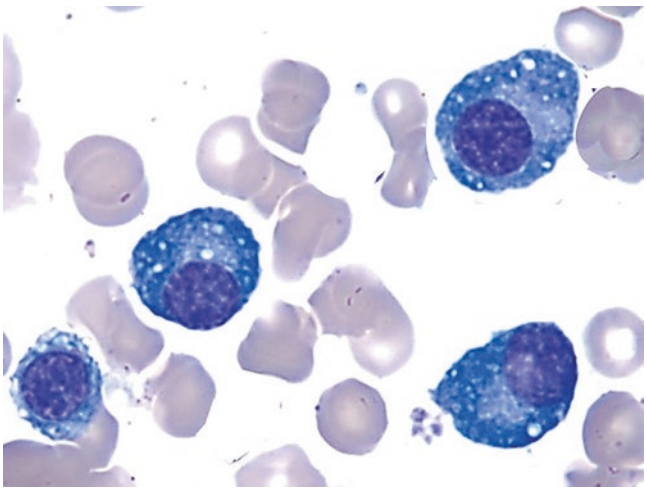


Fig. 1.19 Bone marrow aspirate smear shows three mature plasma cells as well as one polychromatophilic normoblast (left bottom). Plasma cells are medium-sized (8–20 μm), round to oval cells with a moderate amount of deep basophilic cytoplasm, an eccentric, round nucleus, coarse, clumped chromatin, often with a wheel-like pattern, a prominent perinuclear hof, called the Golgi zone, or pale staining in the perinuclear cytoplasm, sometimes with small cytoplasmic vacuoles and no nucleoli

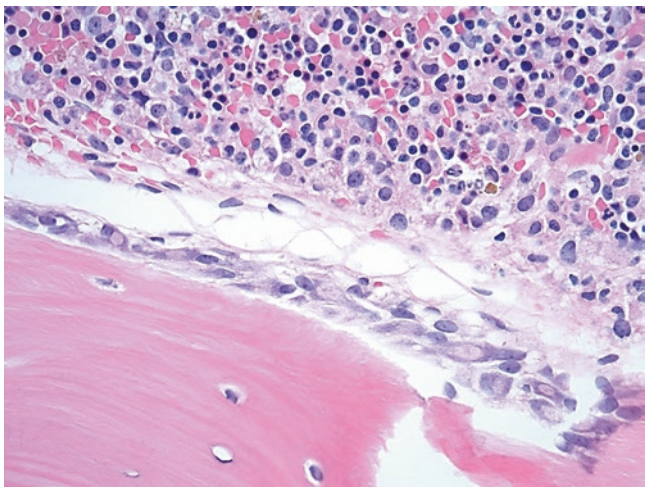


Fig. 1.21 Bone marrow core biopsy section from a child illustrates osteoblasts lining the trabecula, osteocytes within bone lacunae, and hematopoietic cells from immature granulocytic cells near the trabecula to maturing granulocytes and erythroid precursors in the central intramedullary region. Osteoblasts have an eccentric nucleus with distinct Golgi apparatus (hof) away from the nucleus; some show small nucleoli

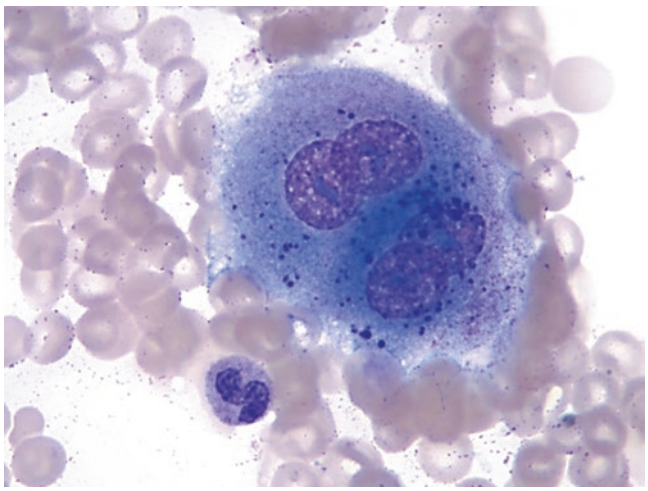


Fig. 1.22 Bone marrow aspirate smear shows an osteoclast and a segmented neutrophil. Osteoclasts, cells involved in the resorption of bone, are very large cells (> 100 μm) with oval to irregular shape, abundant cytoplasm, and coarse granules with variable blue, reddish-purple, or pale pink staining; distinct, multiple nuclei, which are relatively uniformly shaped and widely separated with reticular chromatin, and one or more prominent nucleoli. As multinucleated, giant cells, osteoclasts need to be differentiated from megakaryocytes, metastatic tumor cells, and macrophages. Osteoclasts differ from megakaryocytes by their large size, widely separated nuclei, and coarse cytoplasmic granules with variable staining

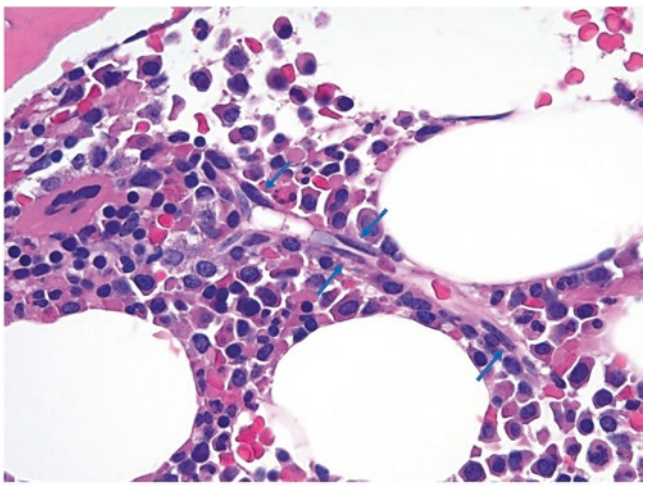


Fig. 1.24 Bone marrow core biopsy section shows endothelial cells lining a sinusoid and trilineage hematopoietic maturation. *Blue arrows* indicate the nucleus of the endothelial cells. Endothelial cells lining sinuses or capillaries are large, elongated cells (20–30 μm) with a moderate amount of pink to light blue cytoplasm, an oval to elongated nucleus with tapering of both ends of the nucleus, dense chromatin, and small, variable nucleoli

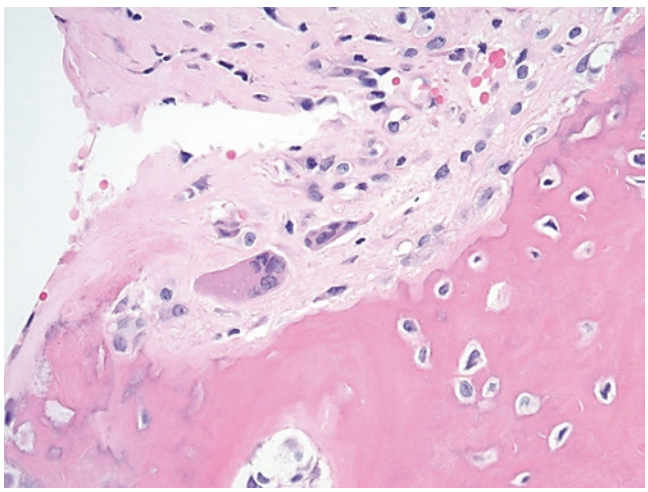


Fig. 1.23 Bone marrow core biopsy section from a child shows two large osteoclasts with multiple separate nuclei and abundant cytoplasm, adjacent to bone trabecula

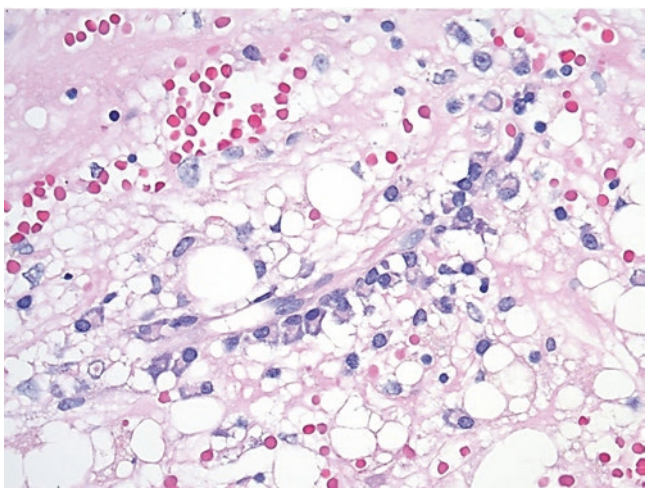


Fig. 1.25 Bone marrow core biopsy section shows marrow stroma composed of sinusoid, endothelial cells, plasma cells (scattered as single cells or in a perivascular location), histiocytes, lymphocytes, and adipose cells in a hypocellular marrow

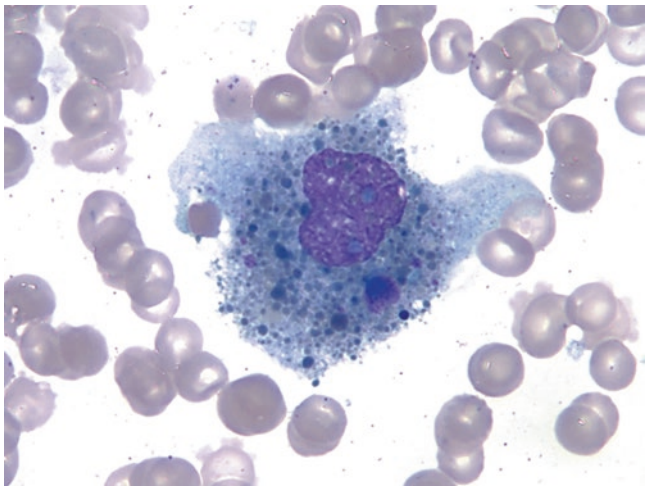


Fig. 1.26 Bone marrow aspirate smear shows a macrophage (or histiocyte). Macrophages involved in phagocytosis are large cells (15–80 μm) with an irregular shape and shaggy margins, abundant blue to pale-pink cytoplasm with large, amorphous debris or phagocytosed materials, often vacuoles, azurophilic granules and pseudopodia, an eccentric nucleus with reticulated chromatin, and one or more small nucleoli

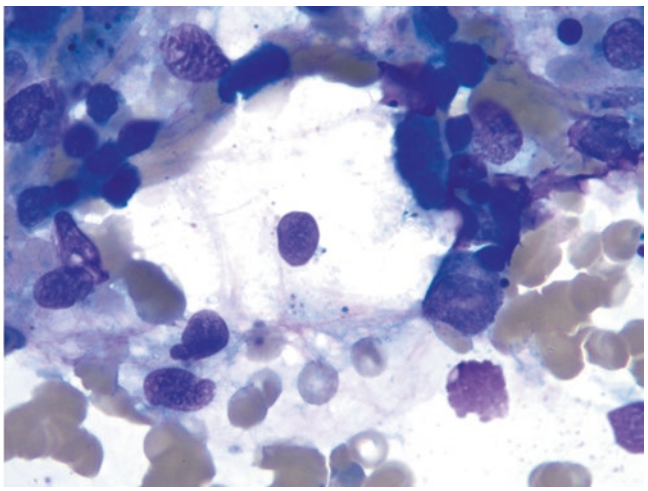


Fig. 1.28 Bone marrow aspirate smear shows a large adipocyte (adipose cell) at the center, surrounded by hematopoietic cells. Adipocytes are very large (25–80 μm), with abundant pale blue to colorless cytoplasm containing numerous large fat vacuoles and delicate eosinophilic fibrils. They often have an eccentric, small, oval to round nucleus, dense chromatin, and small nucleoli

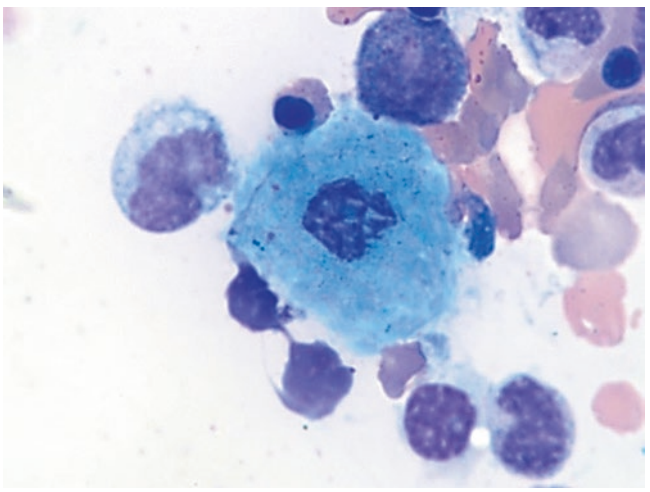


Fig. 1.27 Bone marrow aspirate smear shows a sea-blue histiocyte at the center. This histiocyte (20–60 μm) has abundant cytoplasm with variably blue or blue-green pigments or globules that contain an insoluble lipid pigment called *ceroid*. Small numbers of sea-blue histiocytes can be observed in normal bone marrow

Suggested Reading

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