Reactive Changes

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Recognition of bone marrow pathology requires an understanding not only of normal marrow cytology and architecture but also of the myriad ways in which the marrow can change in response to extramedullary insults or stimuli. Reactive marrow changes can be quantitative (hyperplasia or hypoplasia) or qualitative (left-shifted maturation, cytologic atypia), and they can affect one or multiple hematopoietic lineages as well as the lymphoid, histiocytic, or stromal marrow compartments (Figs. 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24, 2.25, 2.26, 2.27, 2.28, 2.29, 2.30, 2.31, 2.32, 2.33, 2.34, 2.35, 2.36, 2.37, 2.38, 2.39, 2.40, 2.41, 2.42, 2.43, 2.44, 2.45, 2.46, 2.47, and 2.48).

Causes of reactive bone marrow changes typically originate outside of the marrow itself. The differential diagnosis for many of the changes illustrated includes autoimmune disease (Figs. 2.3, 2.4, 2.5, 2.18, 2.19, and 2.26), nutritional deficiency or excess (Figs. 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.15, 2.16, and 2.17), toxic insults, medications (*see* Chap. 3), and infections (*see* Chap. 5; Fig. 2.22).

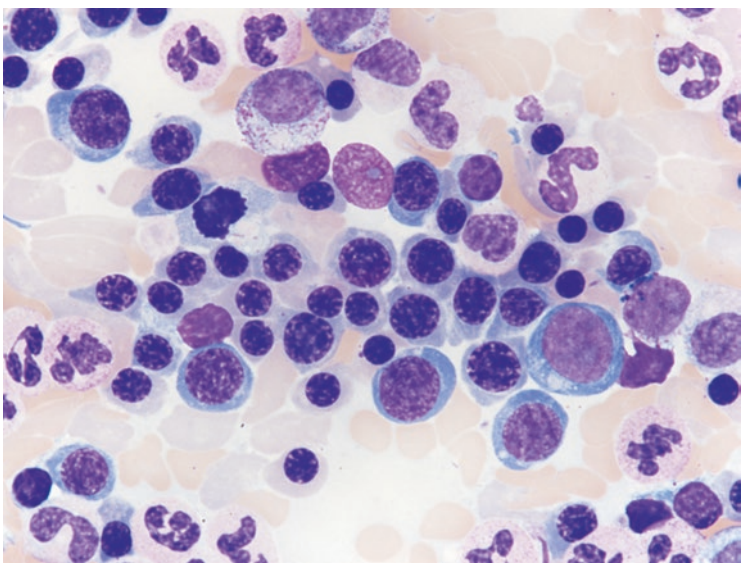

Fig. 2.1 Erythroid hyperplasia can be seen as a normal response to anemias of various causes, particularly those involving peripheral red blood cell (RBC) destruction, sequestration, or bleeding. Increased erythropoietin secretion, from either a normal physiologic response to a hypoxic state or inappropriate secretion by various tumors, may also lead to erythroid hyperplasia. This bone marrow aspirate is from a female patient with metastatic renal cell carcinoma with a hemoglobin of 19.0 g/dL. The serum erythropoietin level was markedly elevated. A bone marrow biopsy was undertaken to exclude a myeloproliferative neoplasm such as polycythemia vera. Aspirate shows an erythroid predominance, but with complete maturation and without cytologic atypia. Molecular studies for *JAK2*, *CALR*, and *MPL* mutations were negative

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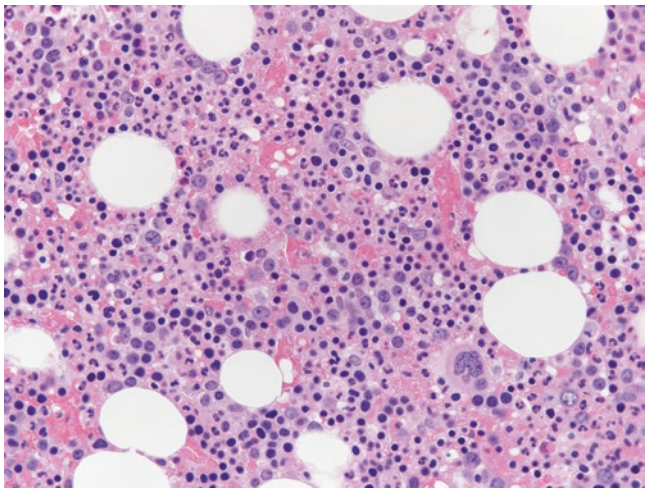

Fig. 2.2 The bone marrow core biopsy specimen from the patient described in Fig. 2.1 shows erythroid hyperplasia with increased numbers of erythroid islands, but with normal and complete maturation

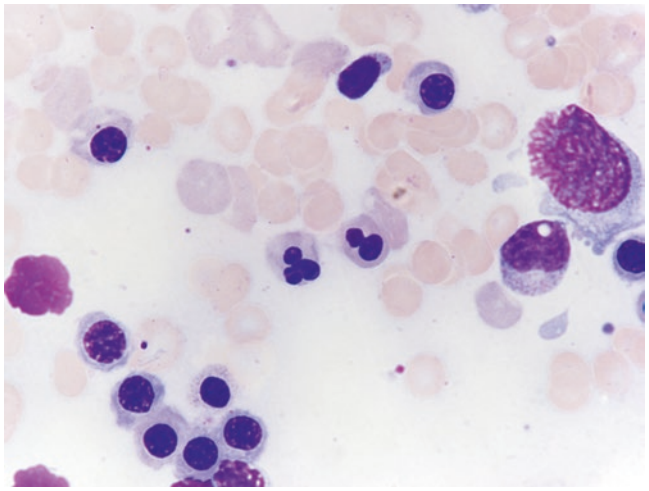

Fig. 2.4 Bone marrow aspirate in a patient with an autoimmune hemolytic anemia. Erythropoiesis may show striking cytologic atypia, akin to that seen in myelodysplasia ("stress dyserythropoiesis"). Shown here are erythroid precursors with nuclear irregularity and budding. Clinical history, as well as morphologic evaluation of the other lineages, is critical to avoid a misdiagnosis of myelodysplastic syndrome in this setting

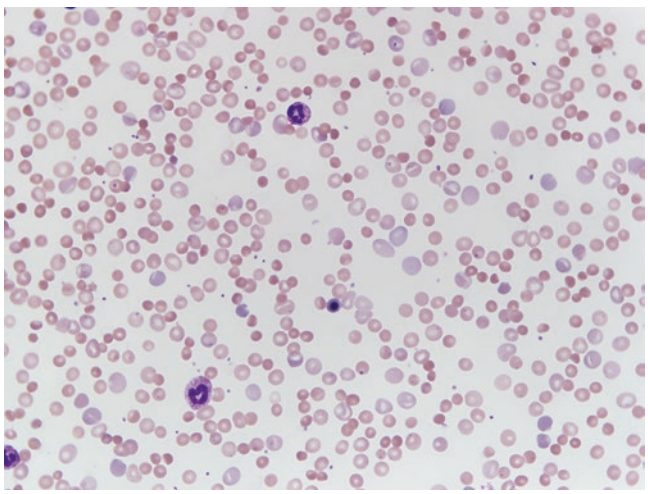

Fig. 2.3 Erythroid hyperplasia can accompany peripheral RBC destruction, as in this patient with an autoimmune hemolytic anemia. Peripheral blood smear showing marked increase in polychromatophilic RBCs, spherocytes, and circulating nucleated RBCs

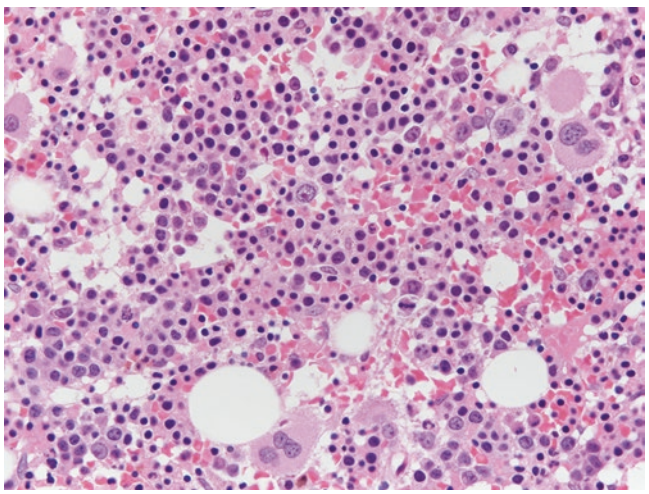

Fig. 2.5 Bone marrow biopsy in a patient with an autoimmune hemolytic anemia shows hypercellularity secondary to erythroid hyperplasia

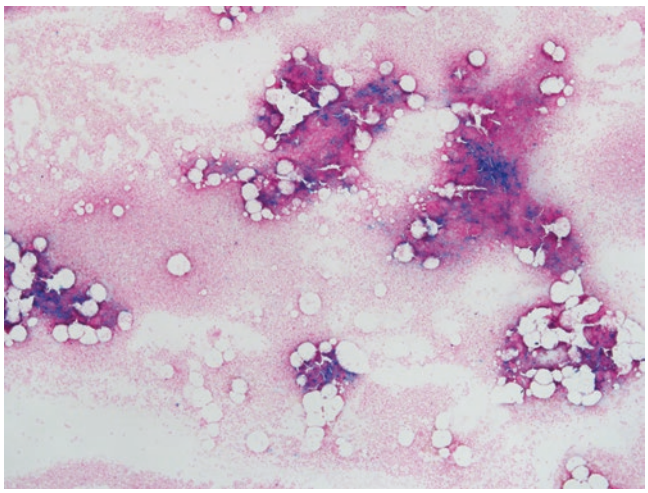

Fig. 2.6 Prussian blue iron stain on a bone marrow aspirate smear from a patient with anemia of chronic disease, showing increased storage iron (*blue*)

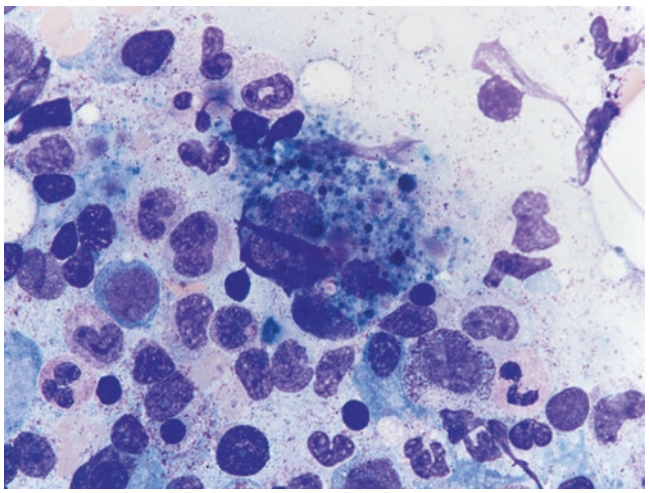

Fig. 2.8 Bone marrow aspirate in a patient with anemia of chronic disease. The macrophage contains chunky hemosiderin granules, which appear blue-black on Wright-Giemsa stain

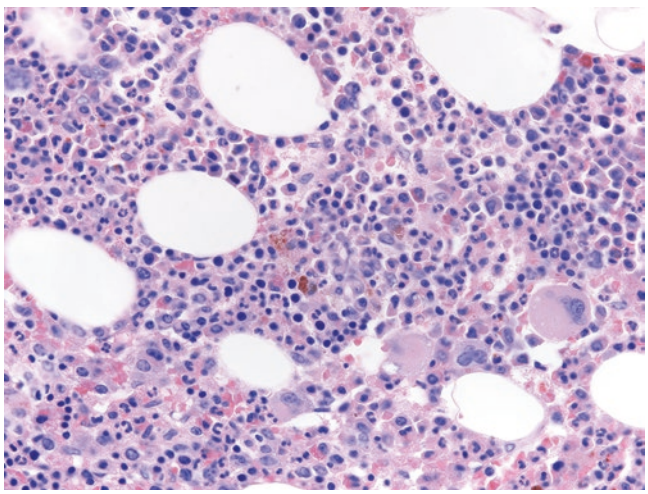

Fig. 2.7 Bone marrow core biopsy in a patient with anemia of chronic disease demonstrates increased hemosiderin-laden macrophages

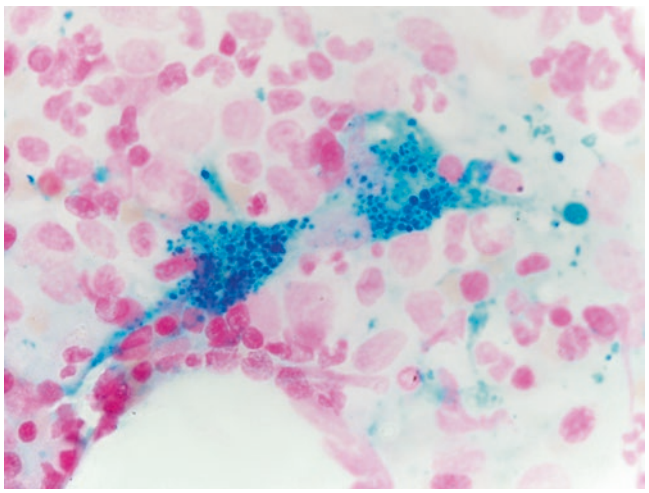

Fig. 2.9 This higher-power image of Prussian blue stain shows iron within a macrophage from the same patient as depicted in Fig. 2.8

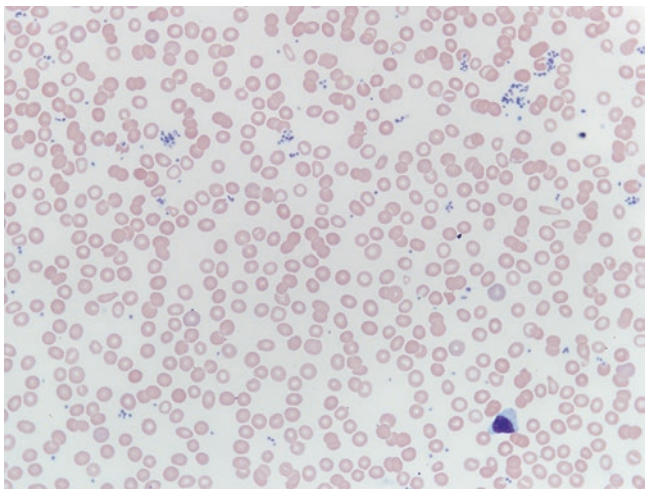

Fig. 2.10 Iron deficiency anemia is common and presents with typical CBC and peripheral smear findings, usually not requiring bone marrow biopsy. Shown here is an example of a peripheral blood smear in a patient with iron deficiency anemia (hemoglobin 9.2 g/dL, MCV 76.0 fL). Reactive thrombocytosis is often seen, along with characteristic elongated elliptocytes ("pencil cells") and hypochromic, microcytic RBCs

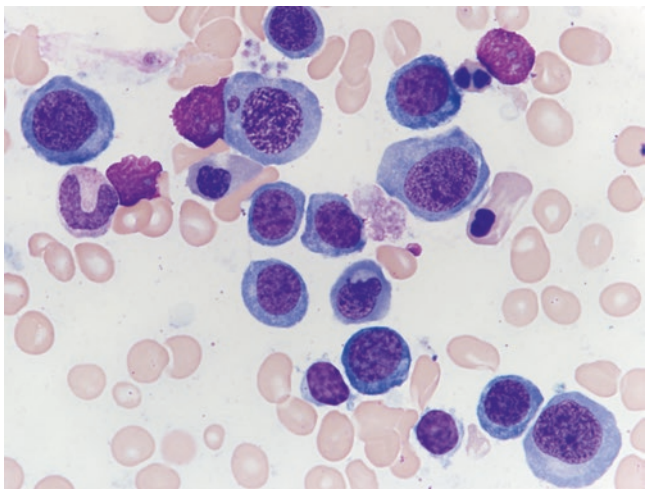

Fig. 2.12 Bone marrow aspirate in a patient with vitamin B12 deficiency and megaloblastic anemia (hemoglobin 7.3 g/dL, MCV 121.6 fL). Note the characteristic megaloblastic erythroid maturation. Erythroid precursors show nuclear-cytoplasmic dyssynchrony and are left shifted. Abnormally large nuclei show abnormal chromatin described as "sievelike," "sausage-like," or "ropey." Occasional nuclear budding and terminal dyserythropoiesis are also seen here and may be mistaken for a myelodysplastic process if the clinical history and other characteristic morphologic features are not appreciated

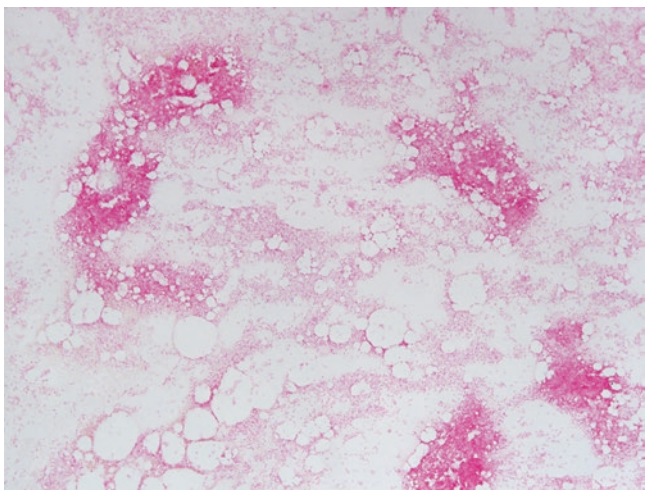

Fig. 2.11 Although bone marrow is not typically required for a diagnosis of iron deficiency anemia, a Prussian blue stain for iron on bone marrow aspirate is still considered the "gold standard" for assessment of iron deficiency [1]. Absence of stainable iron (*blue*) is shown here in a patient with iron deficiency anemia

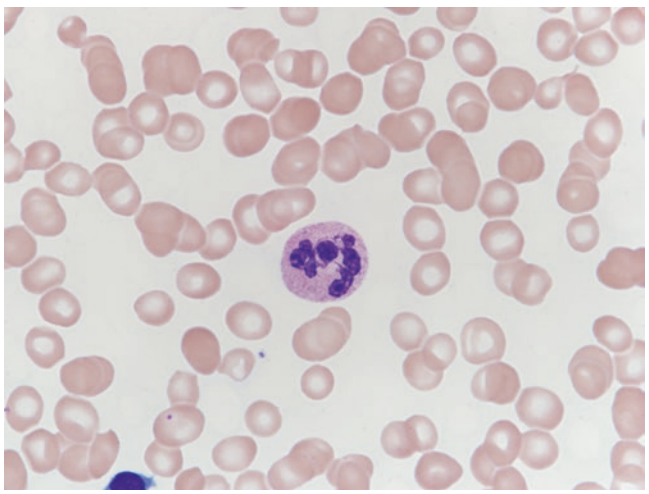

Fig. 2.13 In vitamin B12 deficiency, the granulocytic lineage is also affected, with hypersegmented neutrophils being a characteristic morphologic finding in the peripheral blood and sometimes in the bone marrow

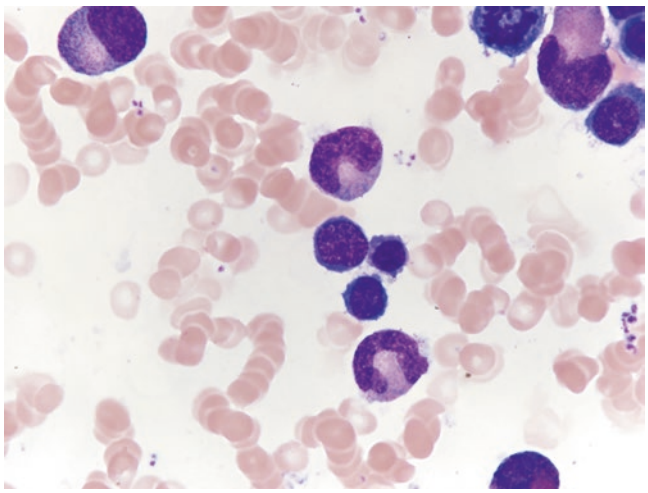

Fig. 2.14 Giant bands ("horseshoe") and metamyelocytes are another common feature of vitamin B12 deficiency

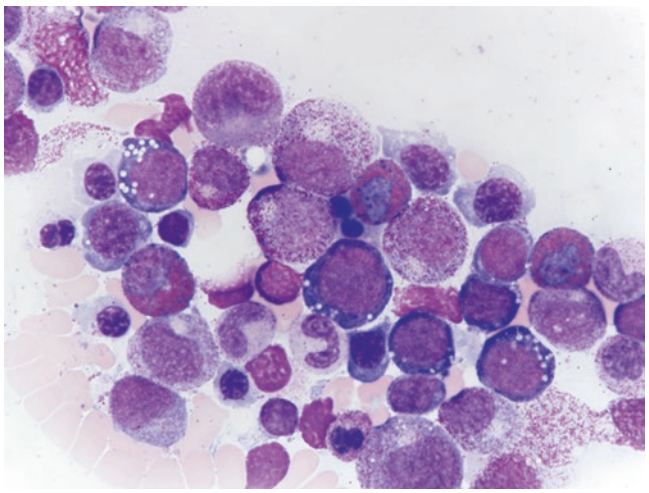

Fig. 2.16 Copper deficiency (often caused by over-ingestion of zinc) can cause cytopenias with peripheral blood and bone marrow features mimicking myelodysplastic syndrome. Erythroid hyperplasia with characteristic cytoplasmic vacuolization in both erythroid and granulocytic precursors is a hallmark finding

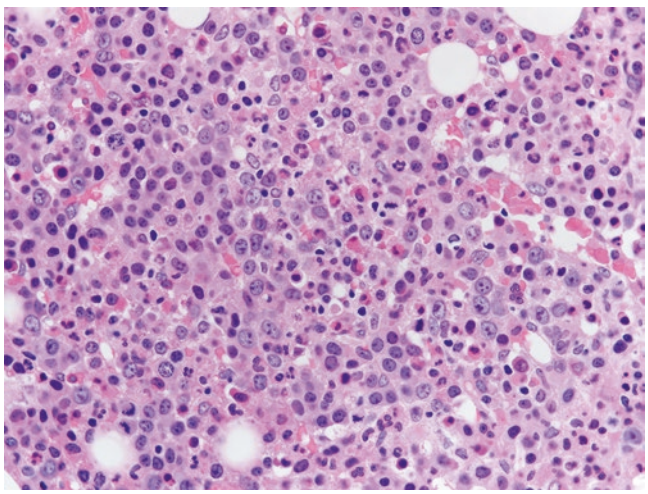

Fig. 2.15 The bone marrow core biopsy in vitamin B12 deficiency often is markedly hypercellular for the patient's age. Note the left-shifted appearance to the erythroid lineage, with prominent erythroblasts containing fine chromatin. Granulocytes are also left shifted, but with complete maturation. These features are nonspecific and could be misconstrued as a myeloid neoplasm

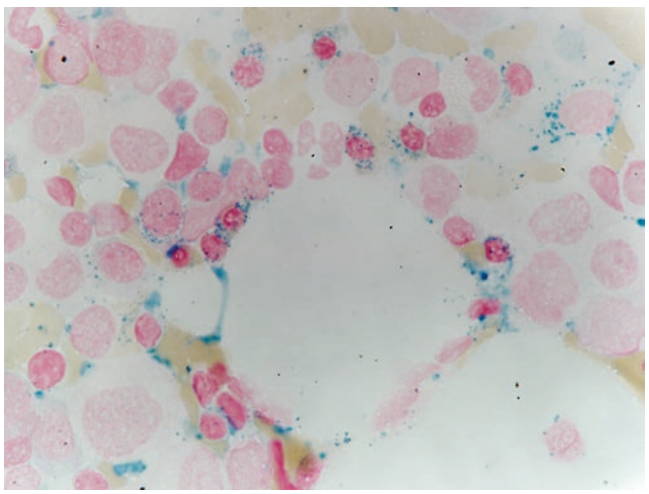

Fig. 2.17 Common findings in copper deficiency include increased storage iron and ring sideroblasts as shown in this Prussian blue stain, which can lead to misdiagnosis of myelodysplastic syndrome. Nonneoplastic causes of ring sideroblasts include alcoholism, medications (isoniazid), and lead poisoning, as well as congenital sideroblastic anemias [2] (*see* Chap. 4)

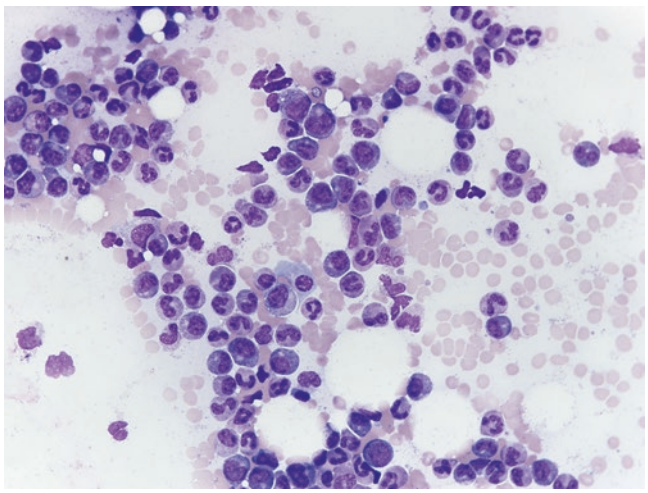

Fig. 2.18 An elevated myeloid to erythroid (M:E) ratio can occur if red cell production is depressed, often in autoimmune or paraneoplastic states. This bone marrow aspirate shows pure red cell aplasia in a patient with a thymoma

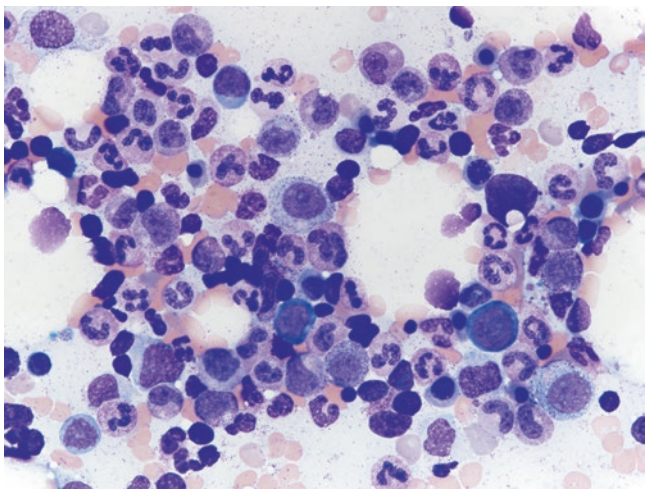

Fig. 2.20 Reactive granulocytic hyperplasia is characteristic of infections, especially bacterial sepsis, and can be seen in other inflammatory settings. Growth factor therapy, also described in Chap. 3, is also a common cause of granulocytic hyperplasia in patients receiving chemotherapy for hematopoietic neoplasms. This bone marrow aspirate shows granulocytic hyperplasia without significant left shift

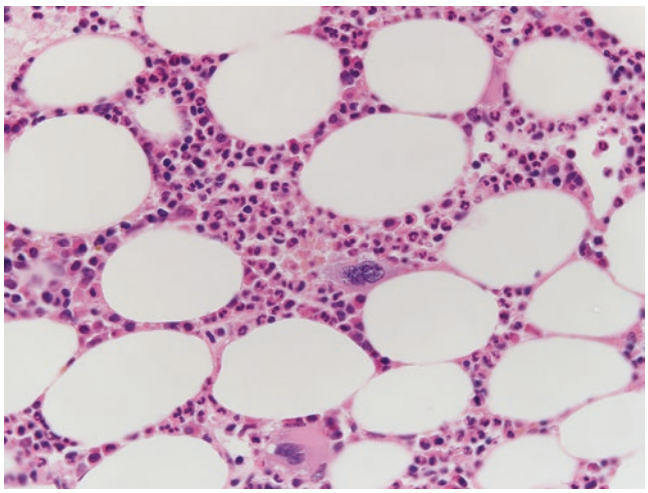

Fig. 2.19 The corresponding bone marrow biopsy specimen from Fig. 2.18 shows pure red cell aplasia in a patient with a thymoma

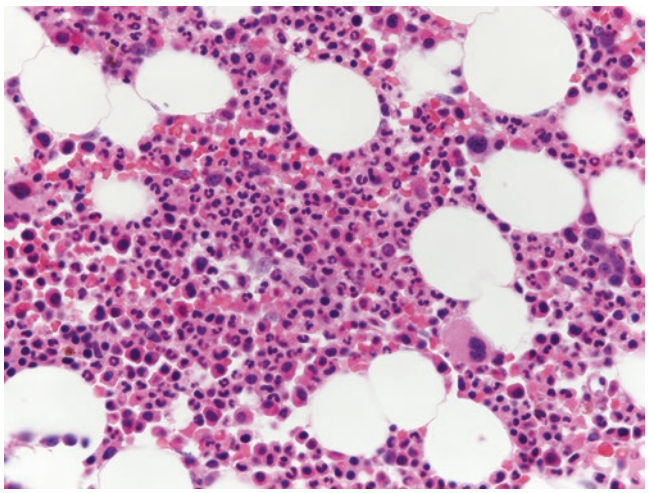

Fig. 2.21 This bone marrow biopsy from the same patient as shown in Fig. 2.20 shows granulocytic hyperplasia with increased numbers of mature granulocytes within the interstitium, away from the trabeculae. Erythroid precursors are also present but are relatively decreased in number

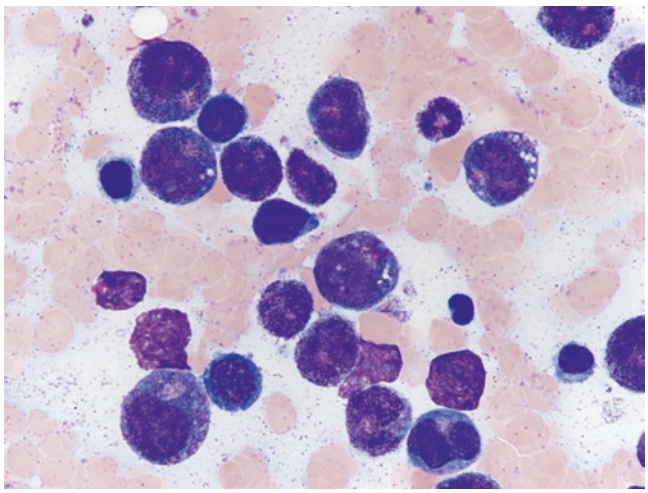

Fig. 2.22 Bone marrow aspirate from a patient with ongoing bacterial sepsis. Granulocytic hyperplasia and left shift are prominent. Toxic granulation and prominence of large, dark purple cytoplasmic granules, as well as vacuoles, are noted in the left-shifted granulocytic precursors

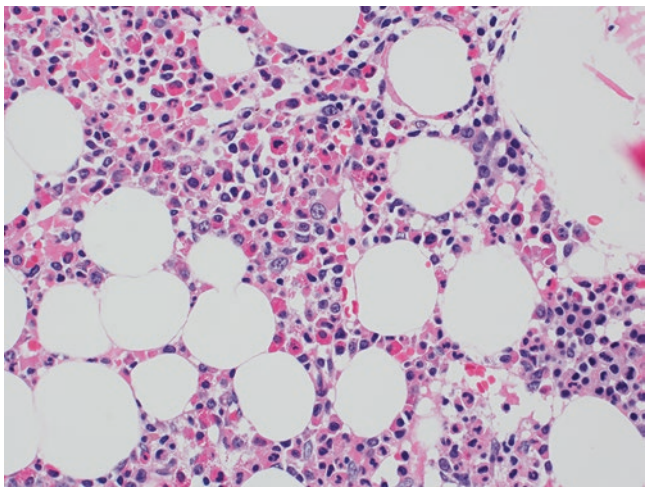

Fig. 2.24 Bone marrow biopsy showing eosinophilia, from the patient in Fig. 2.23

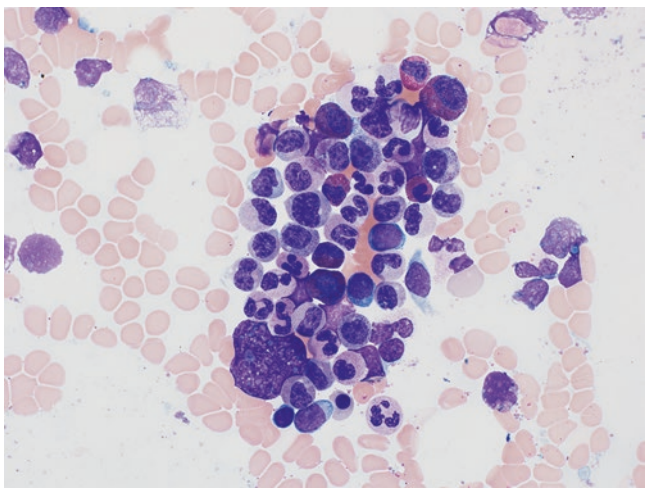

Fig. 2.23 Bone marrow aspirate showing eosinophilia. Eosinophils show normal maturation and cytology. This patient has a history of eosinophilic fasciitis and a peripheral eosinophilia. Increased eosinophils can be associated with a number of hematopoietic malignancies, but they also can be seen in infections, autoimmune disorders, and as a hypersensitivity to drugs or other substances

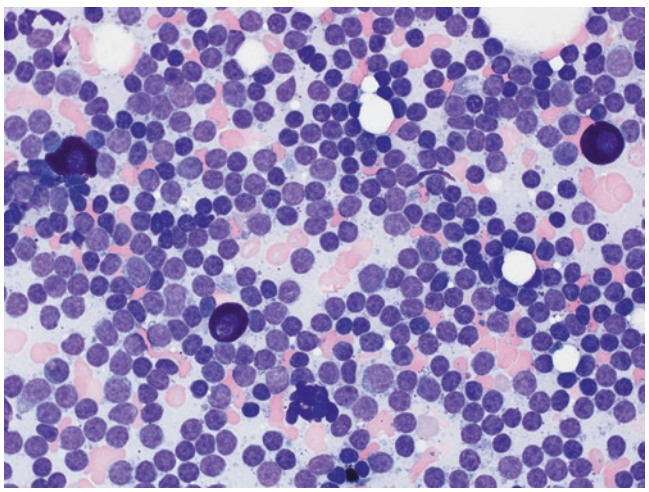

Fig. 2.25 Reactive increases in mast cells are rare in the bone marrow. Indications that mast cells are reactive include normal, round cytology with dense granulation, as depicted in this bone marrow aspirate smear, and a lack of aggregates on core biopsy. Lymphoplasmacytic lymphoma commonly shows a reactive mast cell infiltrate, as shown here

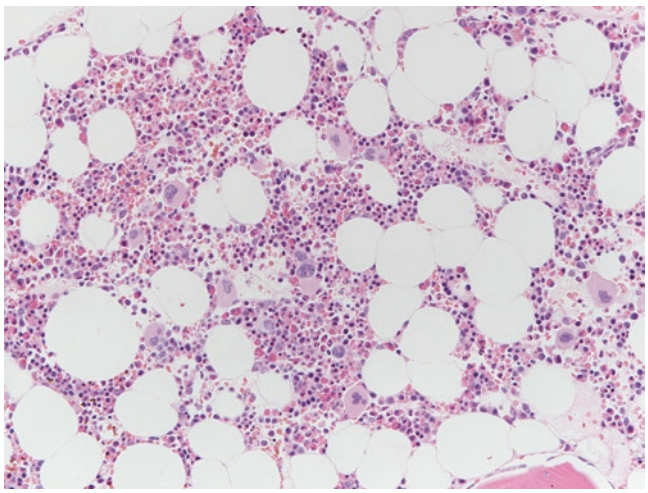

Fig. 2.26 Reactive megakaryocytic hyperplasia is typically seen in the setting of peripheral destruction or sequestration of platelets, such as in immune thrombocytopenic purpura (ITP). Though increased megakaryocytes are seen, they are in varying stages of maturation, lack bizarre cytologic features, and show at most focal loose clustering on biopsy. These features help distinguish a reactive megakaryocytic hyperplasia from that seen in myeloid neoplasms

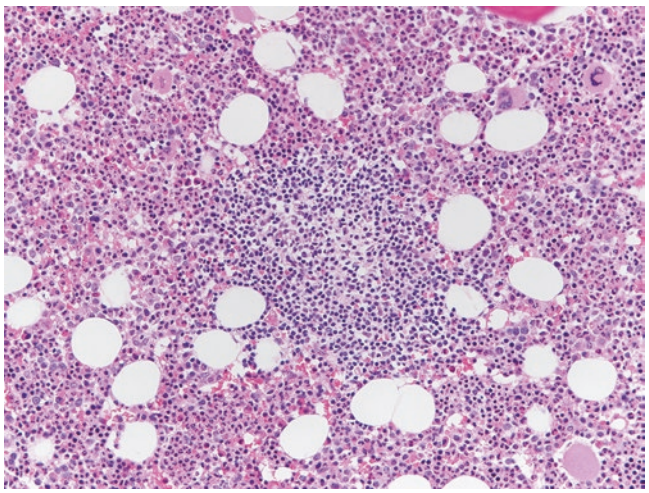

Fig. 2.27 In adults, lymphocytes typically comprise less than 20% of cells in the bone marrow. Reactive lymphoid aggregates in bone marrow increase in frequency with patient age and are typically an incidental finding. Patients with autoimmune disease or active viral infection are more likely to show reactive lymphoid aggregates. Reactive aggregates are typically non-paratrabecular in location and are well-circumscribed, as shown here. Cytologically, the cells are typically small, but there may be rare admixed larger cells, histiocytes, or plasma cells

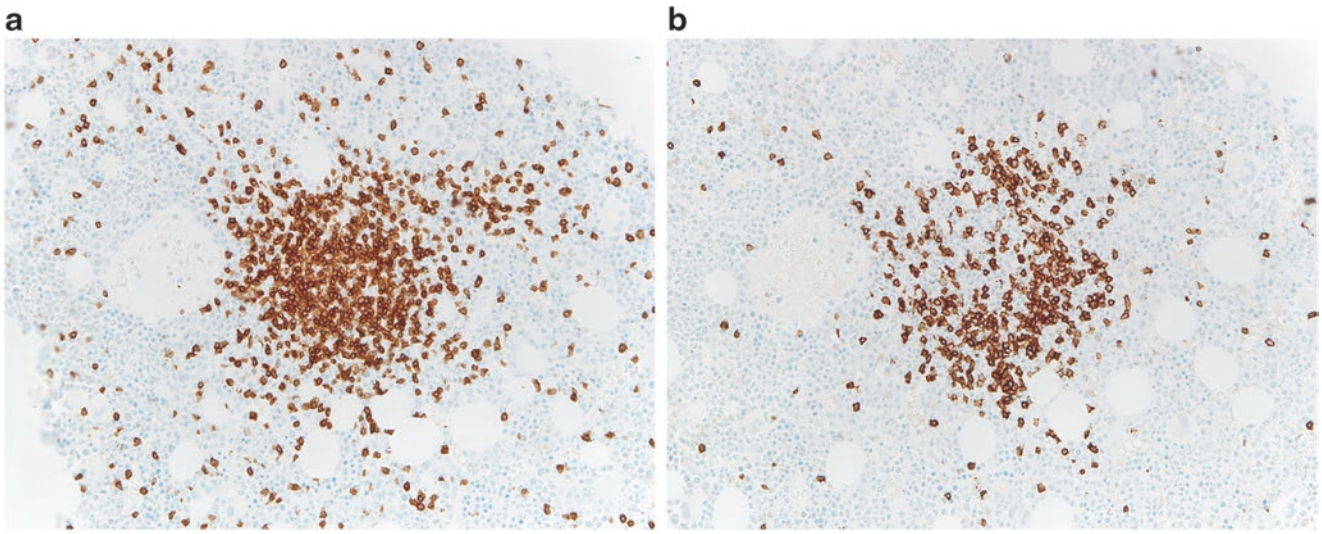

Fig. 2.28 CD3 immunohistochemical stain demonstrates a predominance of T cells (**a**) with fewer B cells staining with CD20 (**b**) in this reactive lymphoid aggregate

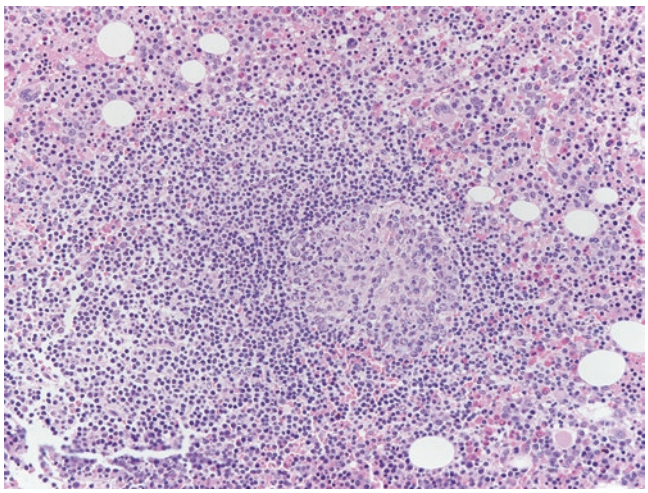

Fig. 2.29 Occasionally in reactive states, germinal center formation may occur in reactive lymphoid aggregates in the bone marrow, especially in autoimmune conditions

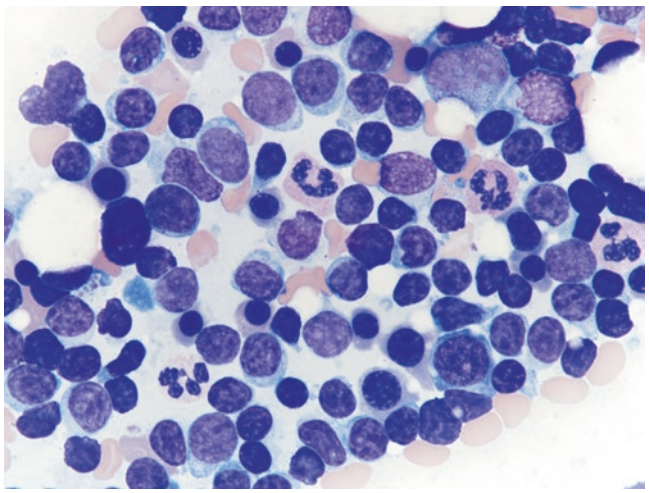

Fig. 2.31 Children may have large numbers of B-cell precursors called *hematogones*. Children (and less often adults) can show hematogone hyperplasia of the bone marrow under certain conditions that stress the bone marrow, including infections, underlying malignancy, and after chemotherapy or bone marrow transplantation. Hematogones can account for more than 50% of cells in rare instances [2]. This bone marrow aspirate demonstrates hematogone hyperplasia in a 64-year-old patient with a history of autoimmune neutropenia. A spectrum of maturation can be seen within the hematogones: some show more immature, blast-like chromatin, and others show more condensed chromatin, smaller size, and more abundant cytoplasm on this Wright-Giemsa-stained aspirate

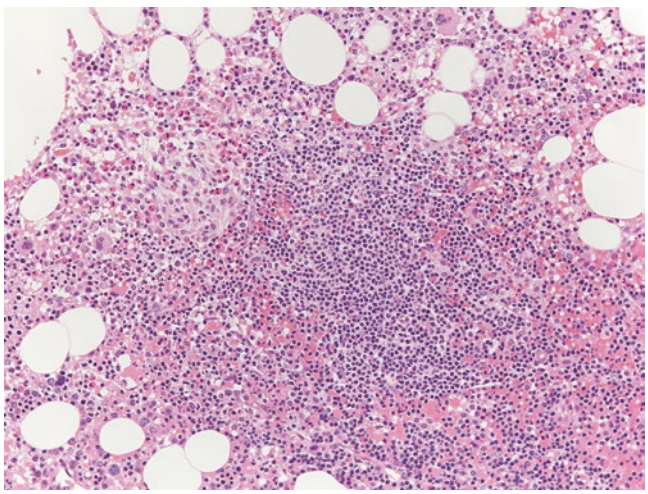

Fig. 2.30 In some instances, reactive lymphoid aggregates can be a clue to an underlying malignancy. Indolent systemic mastocytosis, shown here, often shows mast cell aggregates surrounded by a cuff of small, reactive lymphocytes

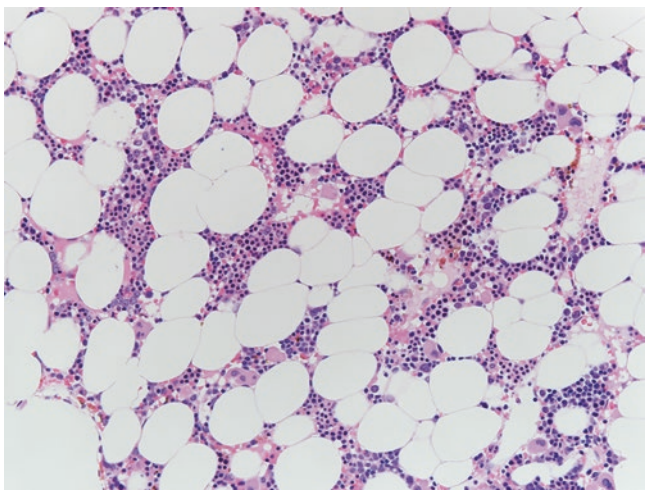

Fig. 2.32 Hematogone hyperplasia. Core biopsy from the same patient as depicted in Fig. 2.31 shows subtle interstitial lymphocytes, but no large aggregates

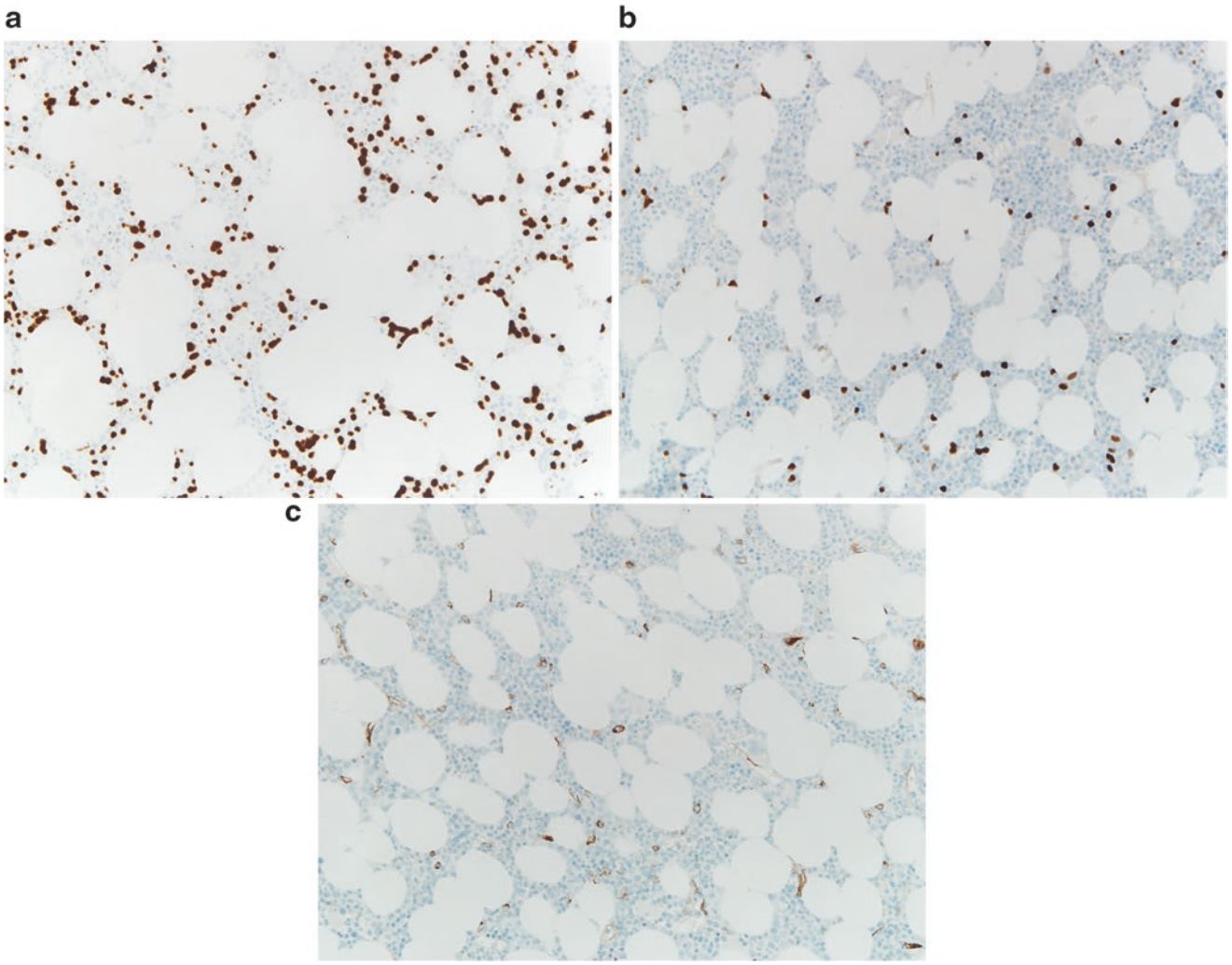

Fig. 2.33 Hematogone hyperplasia. PAX5 immunohistochemical stain shows an increased number of B-cell precursors within the marrow (**a**). In contrast, only rare cells are TdT-positive (**b**) or CD34-positive (**c**), highlighting the spectrum of maturation

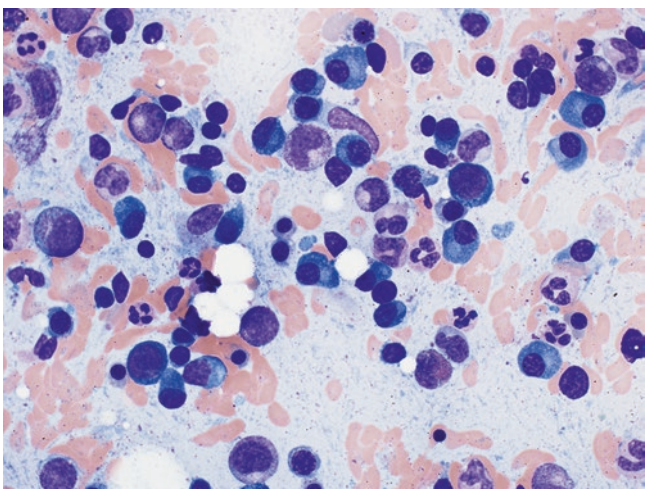

Fig. 2.34 Reactive polyclonal plasmacytosis can uncommonly occur in the bone marrow. Patients may have underlying infection, cirrhosis, autoimmune disease, or other malignancy. Cytologically, the plasma cells are typically bland, but mild atypia such as vacuolization or multinucleation can occur and does not necessarily indicate plasma cell neoplasia. Immunophenotyping is essential to assess for clonality. In this case, polytypic plasma cells account for at least 30% of the marrow cellularity in some areas. The patient had polyclonal hypergammaglobulinemia but no monoclonal protein. Angioimmunoblastic T-cell lymphoma was suspected, but definitive marrow involvement by lymphoma could not be proven

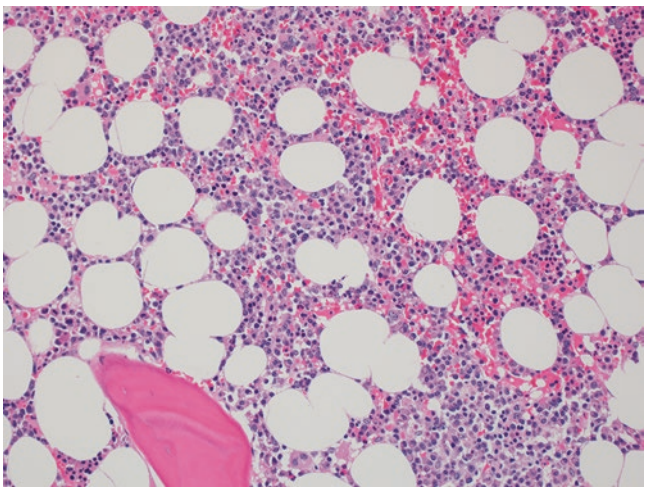

Fig. 2.35 Core biopsy from the patient in Fig. 2.34 shows polytypic plasmacytosis

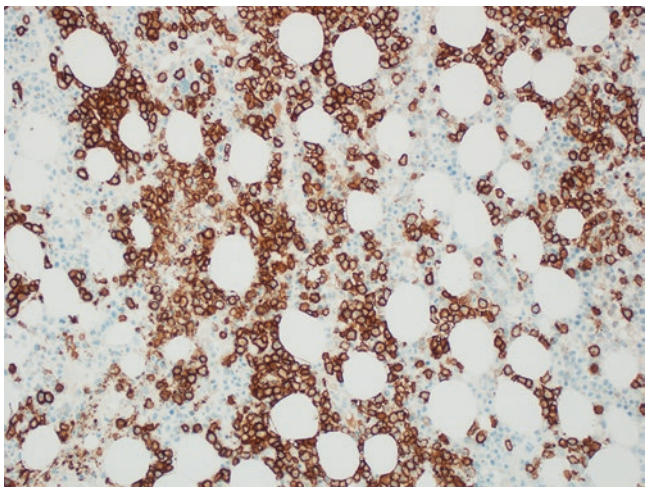

Fig. 2.36 Core biopsy from the patient in Fig. 2.34 shows polytypic plasmacytosis. CD138 immunohistochemistry highlights increased plasma cells

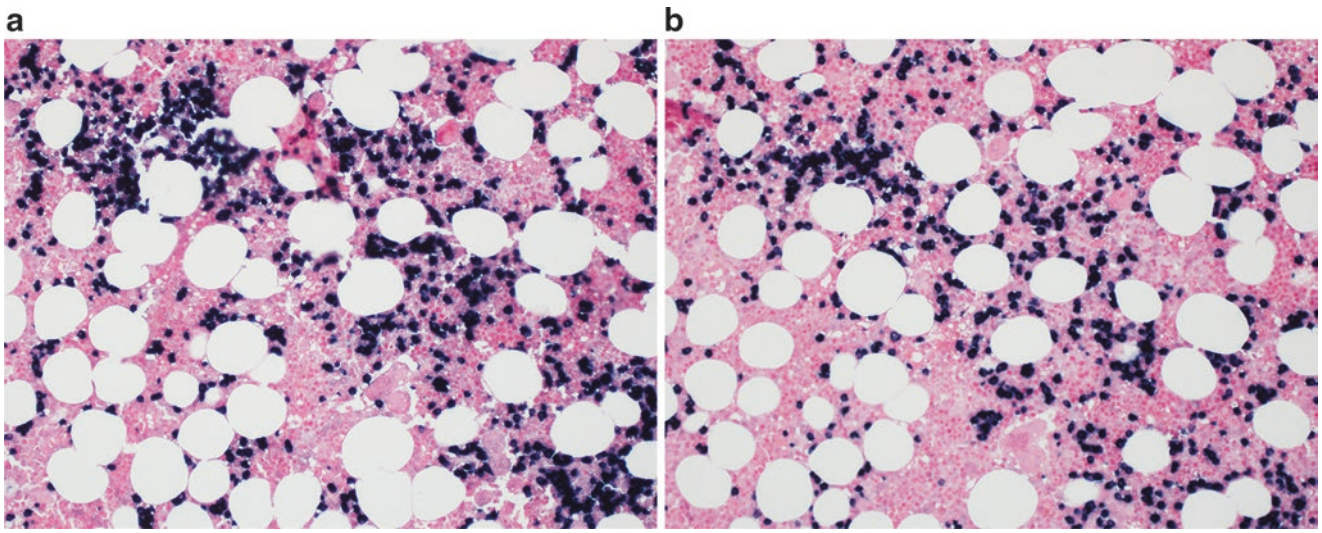

Fig. 2.37 Core biopsy from the patient in Fig. 2.34 shows polytypic plasmacytosis. Kappa (**a**) and lambda (**b**) in situ hybridization shows that the plasma cells are polytypic

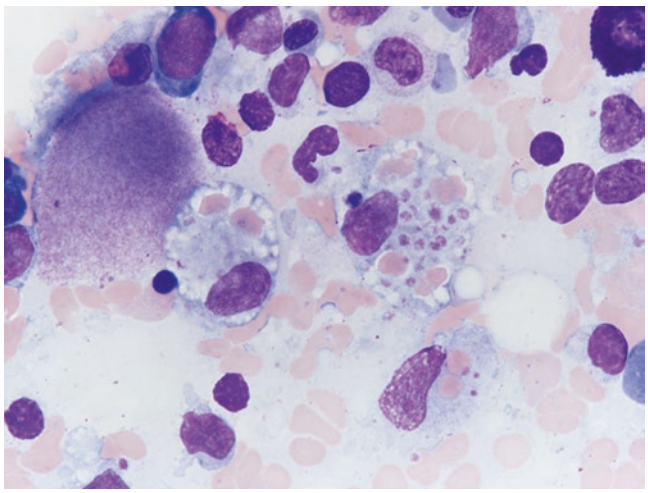

Fig. 2.38 Macrophages normally comprise less than 1% of bone marrow cells [2]. In states of high cell turnover, increased numbers of activated macrophages can be seen in aspirate smears. The presence of increased activated macrophages with ingested intact cells and cellular debris is termed *hemophagocytosis*. This reactive phenomenon can be due to a variety of neoplastic and nonneoplastic causes, including congenital syndromes, lymphoma, autoimmune disease, and viral infection. This aspirate smear shows hemophagocytosis in a patient who was diagnosed with hemophagocytic lymphohistiocytosis (HLH) associated with Epstein-Barr virus (EBV) infection. Examples of familial HLH can be found in Chap. 4 (Constitutional, Metabolic, and Related Disorders), with additional examples and discussion in Chap. 14 (Histiocytic Disorders)

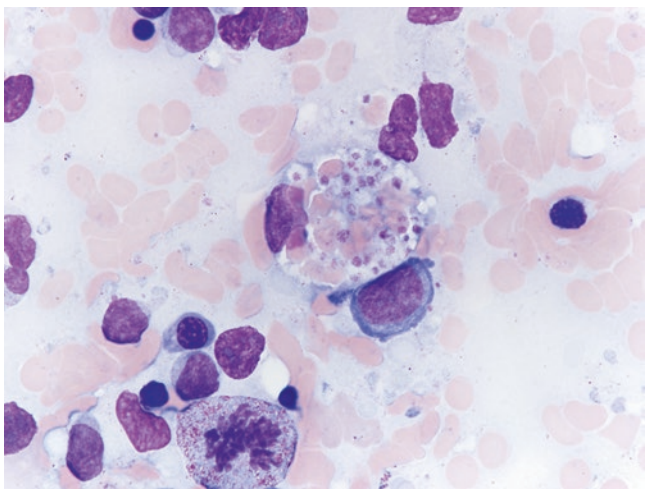

Fig. 2.39 Hemophagocytosis in a patient with HLH; activated macrophage is seen ingesting numerous platelets and RBCs

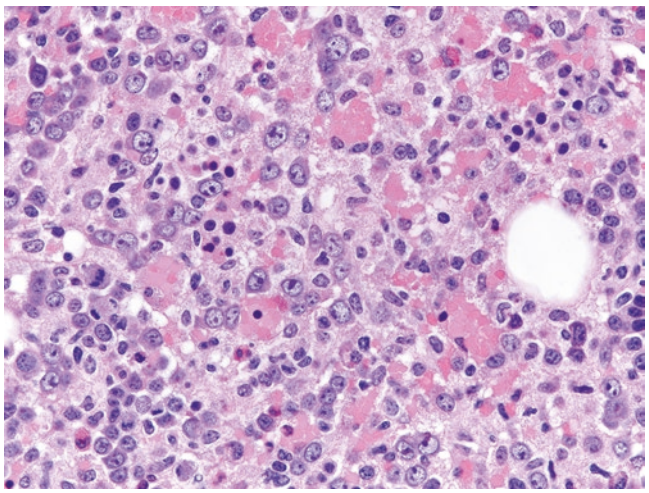

Fig. 2.40 Core biopsy in a patient with HLH, demonstrating increased interstitial macrophages containing ingested cells and cell debris. Especially prominent are macrophages ingesting numerous nonnucleated RBCs

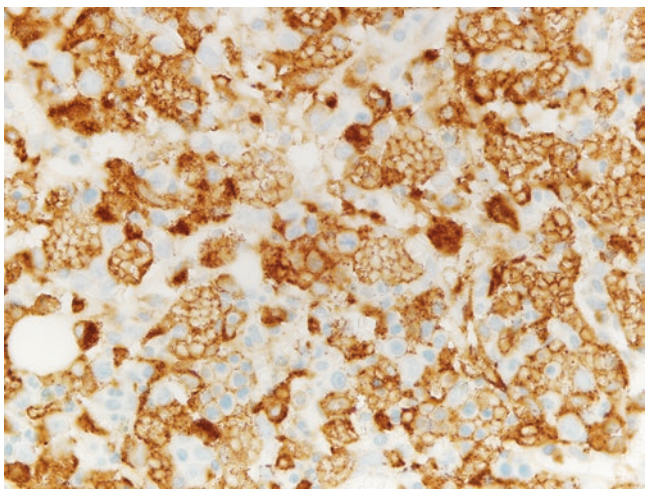

Fig. 2.41 CD163 immunohistochemical stain on the core biopsy stain macrophages and shows increased hemophagocytosis in HLH

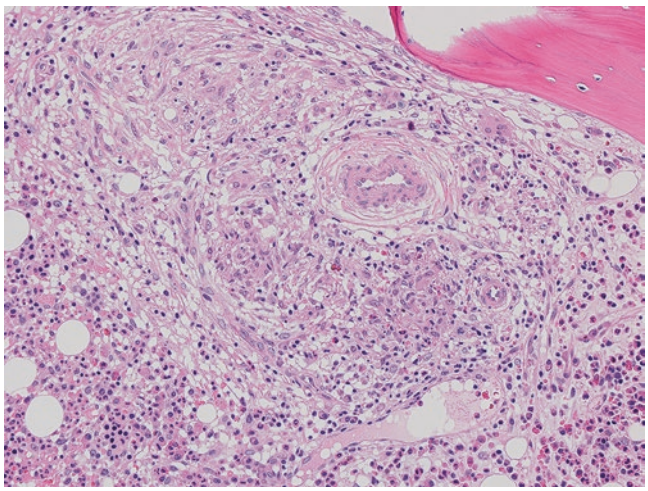

Fig. 2.42 Granulomatous inflammation in the marrow can indicate infection, underlying malignancy, or a systemic inflammatory disease such as sarcoidosis. Shown here are nonnecrotizing granulomas involving the marrow in a patient with sarcoidosis (see Chap. 14 for additional examples)

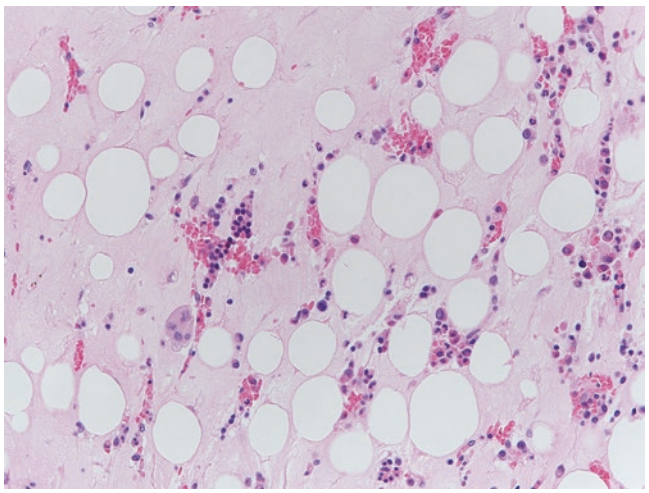

Fig. 2.44 Higher-power image of gelatinous transformation. Fat cell atrophy and loss of marrow elements are characteristic features

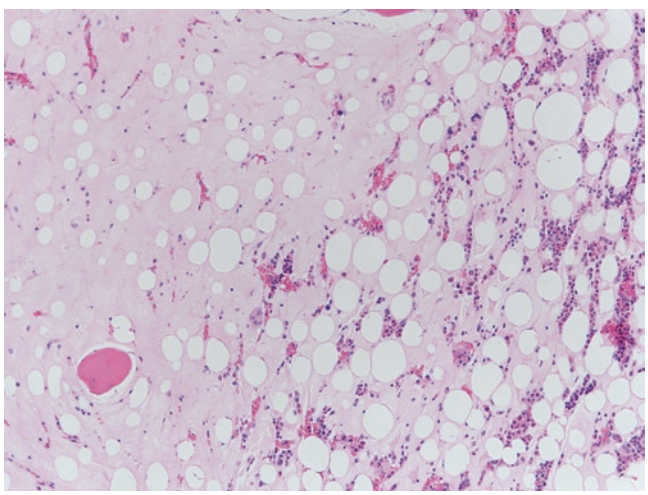

Fig. 2.43 Gelatinous transformation of bone marrow is seen in anorexia nervosa and other malnutritional states. Changes in the bone marrow stroma have been demonstrated to correlate with the degree of weight loss [3]. Bone marrow biopsy demonstrates loss of marrow elements and prominent extracellular deposition of an amorphous, gelatinous-appearing matrix

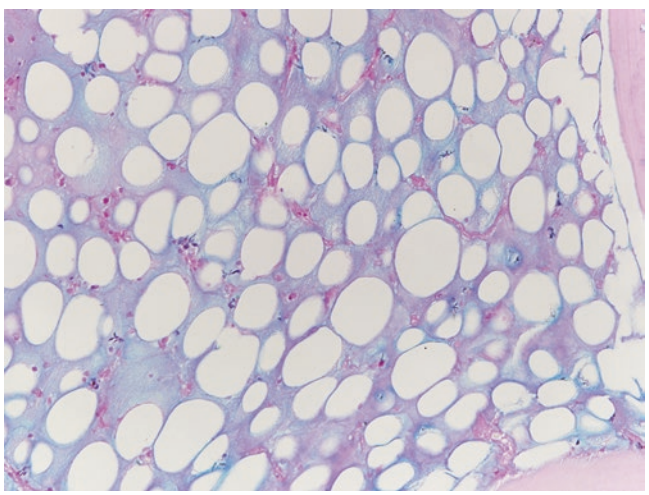

Fig. 2.45 Bone marrow biopsy from a patient with anorexia nervosa. The extracellular matrix seen in states of cachexia is composed of hyaluronic acid, which stains blue on Alcian blue stain as shown here [4]. This stain may aid in distinction from other extracellular deposits such as amyloid

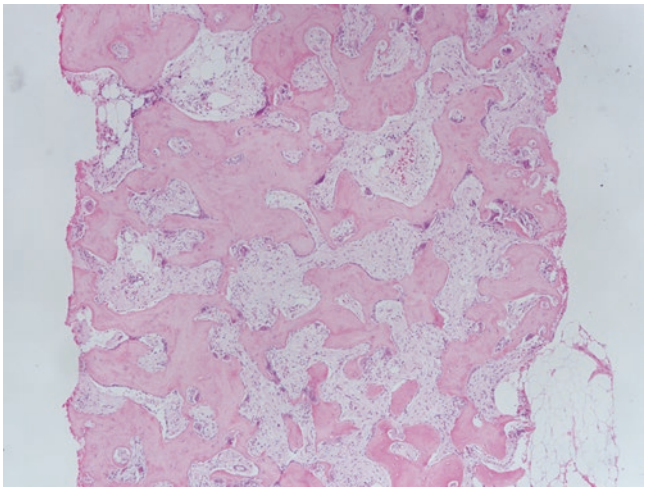

Fig. 2.46 Paget disease of bone (osteitis deformans) is a rare, progressive disease of unknown etiology resulting in accelerated bone remodeling. Bone marrow biopsy will show thickened trabeculae in a "jigsaw" pattern with prominent osteoclast and osteoblast activity. Marrow space shows replacement by fine fibrosis in the chronic stage of the disease. Clinical history is essential to avoid misdiagnosis as an end-stage myeloproliferative neoplasm

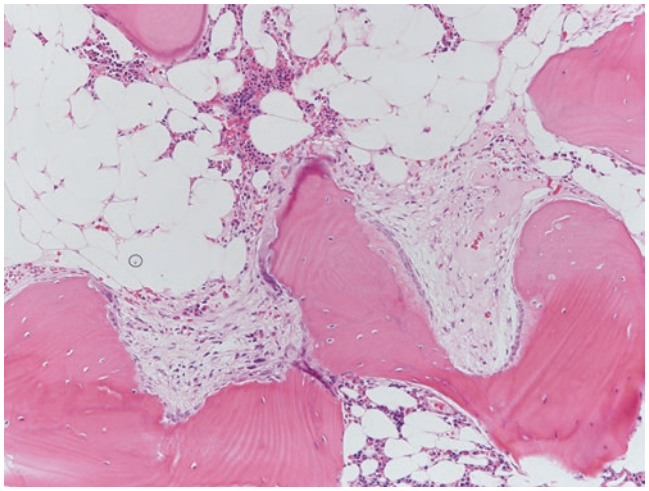

Fig. 2.48 Renal osteodystrophy typically accompanies chronic renal failure. Bone remodeling can be seen with increased osteoclast and osteoblast activity, as well as resulting osteosclerosis. In rare instances, a myelofibrosis-like picture may result [5]

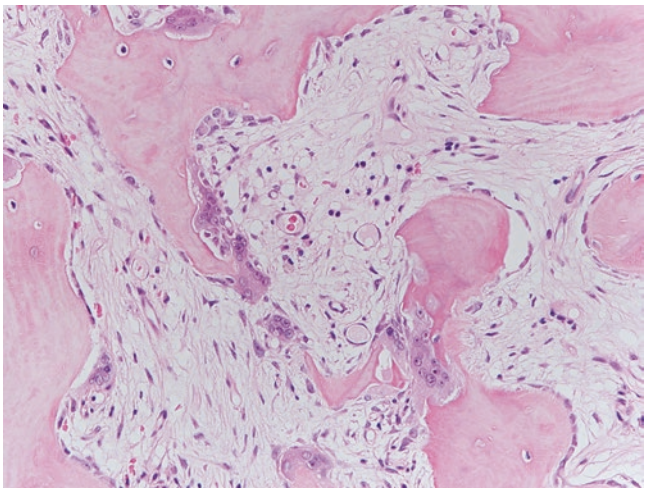

Fig. 2.47 Paget disease of bone (osteitis deformans) at higher power, showing prominent osteoclast and osteoblast activity. Marrow space shows replacement by fine fibrosis in the chronic stage of the disease

In many instances, the morphologic features are nonspecific with regard to etiology, emphasizing the importance of the clinical history in the interpretation of bone marrow pathology. In addition, many reactive changes overlap with those seen in neoplastic conditions, such as the striking erythroid atypia seen in erythroid regeneration in the setting of autoimmune hemolytic anemia (Figs. 2.3, 2.4, and 2.5). Finally, neoplastic conditions involving the marrow can result in a characteristic reactive alteration of other marrow elements, such as the reactive mast cell hyperplasia seen in lymphoplasmacytic lymphoma (Fig. 2.25).

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