Histiocytic Disorders

14

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The Histiocyte Society has revised the classification of histiocytoses and neoplasms of the macrophage and dendritic cell lineages (Table 14.1) [1]. Not all of these disorders involve the bone marrow, but the most common disorders that involve the bone marrow are shown in Figs. 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 14.10, 14.11, and 14.12 and contrasted in Table 14.2.

Langerhans cell histiocytosis (LCH) remains the most characteristic histiocytosis involving the bone marrow; it is generally diagnosed in childhood [2]. The characteristic histologic appearance of LCH is shown in Figs. 14.1, 14.2 and 14.3. It should be noted that a definitive diagnosis requires CD1a and/or CD207 (langerin) staining in the appropriate cells (Fig. 14.2). Although the ultrastructural detection of Birbeck granules is characteristic of LCH, it is no longer required for the diagnosis. Somatic mutations of *BRAF* have been described in a large subset of patients with LCH [3], and immunohistochemical stain for *BRAF* V600E is now available [4].

Histiocytic sarcoma is a rare neoplasm of mature histiocytes, which may involve the bone marrow secondarily (Fig. 14.4). It is important to exclude other neoplasms such as acute monocytic leukemia, lymphomas, carcinomas, and sarcomas before making a diagnosis of histiocytic sarcoma.

Other histiocytic disorders that rarely involve the bone marrow include Rosai-Dorfman disease, with its typical S100 protein-positive histiocytes and emperipolesis [5]; Erdheim-Chester disease, with CD68-positive and S100 protein-/CD1a-negative foamy histiocytes and Touton-type giant cells [6]; follicular dendritic cell sarcoma with CD21-, CD35-, and CD23-positive markers of follicular dendritic cells (FDCs) as shown in Fig. 14.12 [7]; and interdigitating cell sarcoma, in which the tumor cells express S100 protein but lack FDC markers and CD1a [8].

In contrast to these histiocytic neoplasms and the histiocytoses described above, hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndromes are a group of reactive histiocytic disorders in which the clinical and laboratory findings represent a common endpoint of activated histiocytes and immune dysregulation. HLH is classified into primary or familial HLH and secondary or acquired HLH. Secondary hemophagocytic syndromes include those associated with infection, malignancy, and autoimmune disease. The diagnostic criteria for HLH (Table 14.3) were developed for individuals with familial HLH, but these criteria are also used in adults who primarily have secondary HLH [9]. Recent studies have suggested that genetic testing for HLH should be performed in both pediatric and adult patients [10]. Figures 14.5, 14.6, 14.7, 14.8, 14.9, and 14.10 show morphologic evidence of hemophagocytosis for a variety of primary and secondary HLHs. Importantly, morphologic hemophagocytosis is only one criterion for the diagnosis of HLH; by itself, it has little specificity for this disease. Secondary HLH is also associated with autoimmune disease. This is confusing because the term *macrophage activation syndrome* is also used to describe the final pathway of activated histiocytes and immune dysregulation complicating systemic inflammatory disorders, most commonly juvenile idiopathic arthritis and adult-onset Still's disease. Criteria have been published for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis (Table 14.4) [11]; these criteria differ from HLH criteria in that the cytopenias are less severe, ferritin levels are lower, and increased soluble CD25 and decreased/absent NK-cell activity are less commonly observed. Finally, sarcoidosis may rarely involve the bone marrow (Fig. 14.11) [12].

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Table 14.1 Revised classification of histiocytosis and neoplasms of the macrophage-dendritic cell lineage

Group	Entities
L	Langerhans cell histiocytosis (LCH)
	Indeterminate cell histiocytosis
	Erdheim-Chester disease (ECD)
	Mixed ECD and LCH
C	Cutaneous non-LCH histiocytosis
	Cutaneous non-LCH histiocytosis with major systemic component
M	Primary malignant histiocytosis
	Secondary malignant histiocytosis
R	Familial Rosai-Dorfman disease (RDD)
	Classic RDD
	Extranodal RDD
	Neoplasia-associated RDD
	Immune disease-associated RDD
	Other non-C, non-L, non-M, and non-H histiocytoses
H	Primary hemophagocytic lymphohistiocytosis (HLH)
	Secondary HLH
	HLH of unknown/uncertain origin

Adapted from Emile et al. [1]

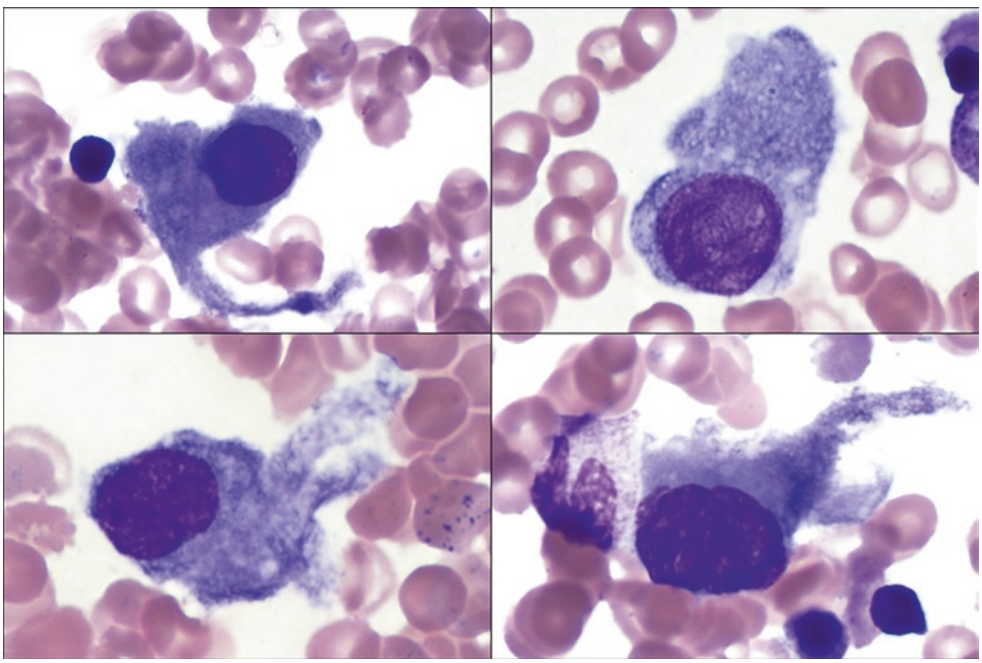

Fig. 14.1 Langerhans cell histiocytosis. This 1-year-old girl presented with anemia of 8.5 g/dL, thrombocytopenia of 42×10^9/L, hepatosplenomegaly, and disseminated intravascular coagulation. A Wright-Giemsa-stained bone marrow aspirate smear revealed scattered histiocytic cells that are large in size, with deeply basophilic cytoplasm showing prominent cytoplasmic processes. The nuclei are round to oval shaped with reticulated chromatin and grooved nuclei. Occasional nucleoli are noted

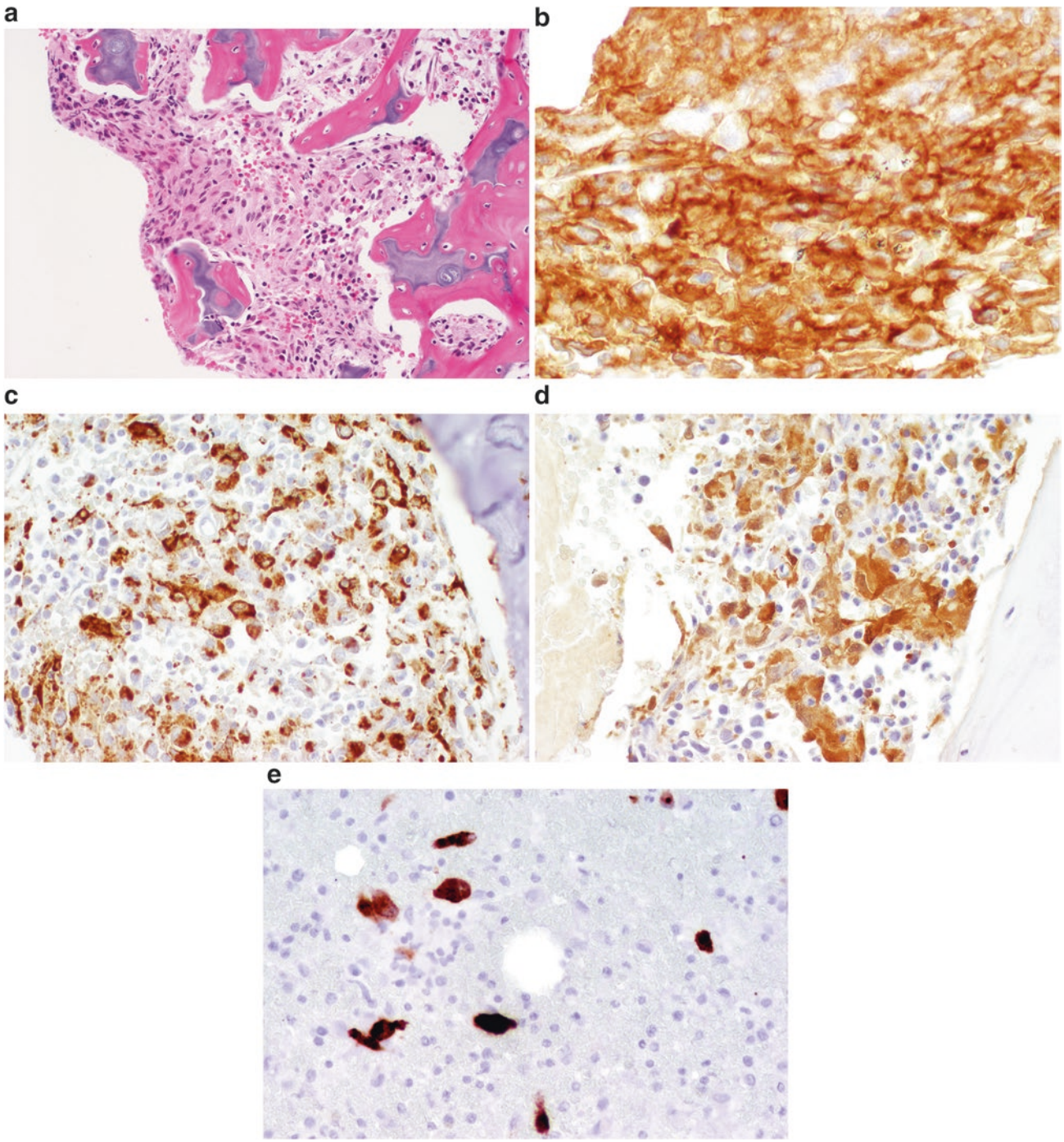

Fig. 14.2 Langerhans cell histiocytosis. (**a**) A hematoxylin and eosin (H&E)-stained bone marrow trephine section reveals an extensive infiltrate of large, clustered cells with abundant eosinophilic cytoplasm and monocytoid nuclei. The bony trabeculae show bony remodeling, as appropriate for a child of this age with incomplete ossification of bone. (**b**) The neoplastic cells show strong and uniform membranous expression with an immunohistochemical stain for CD1a. (**c**) The neoplastic infiltrate demonstrates cytoplasmic and membranous expression of CD68, confirming the histiocytic nature of these cells. (**d**) S100 protein immunostain highlights the neoplastic cells with nuclear and cytoplasmic staining. The elongated cytoplasmic processes can be seen. (**e**) On this bone marrow section, scattered neoplastic cells are also highlighted by an immunohistochemical stain for langerin. The langerin stain shows deep cytoplasmic staining of these cells

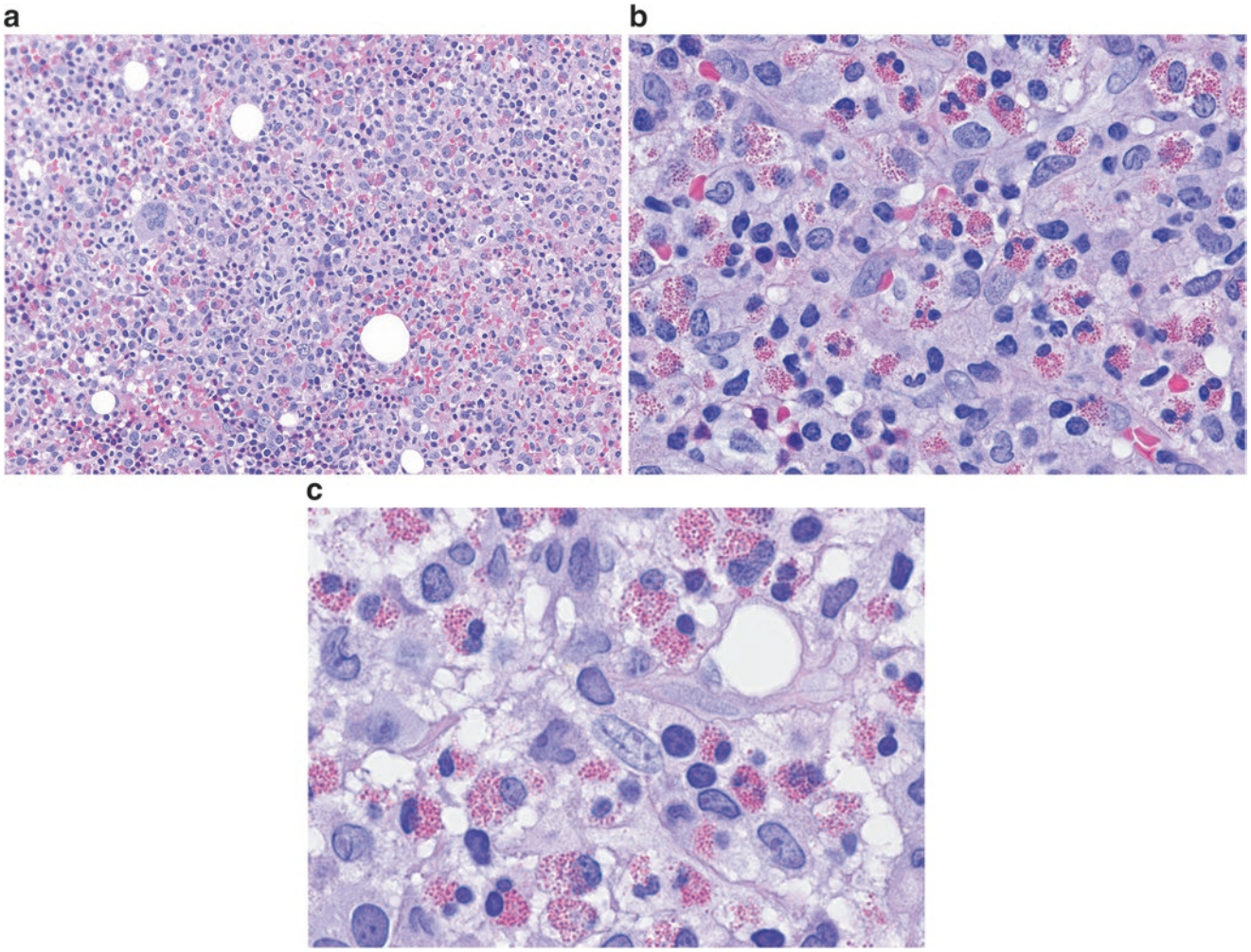

Fig. 14.3 Langerhans cell histiocytosis. (**a**) In this hypercellular bone marrow, a prominent histiocytic infiltrate and eosinophilia are noted. (**b** and **c**) Higher-power views reveal that some histiocytes show characteristic elongated coffee bean-like nuclei with grooved or folded nuclei (*Courtesy of* Luke Shier, MD)

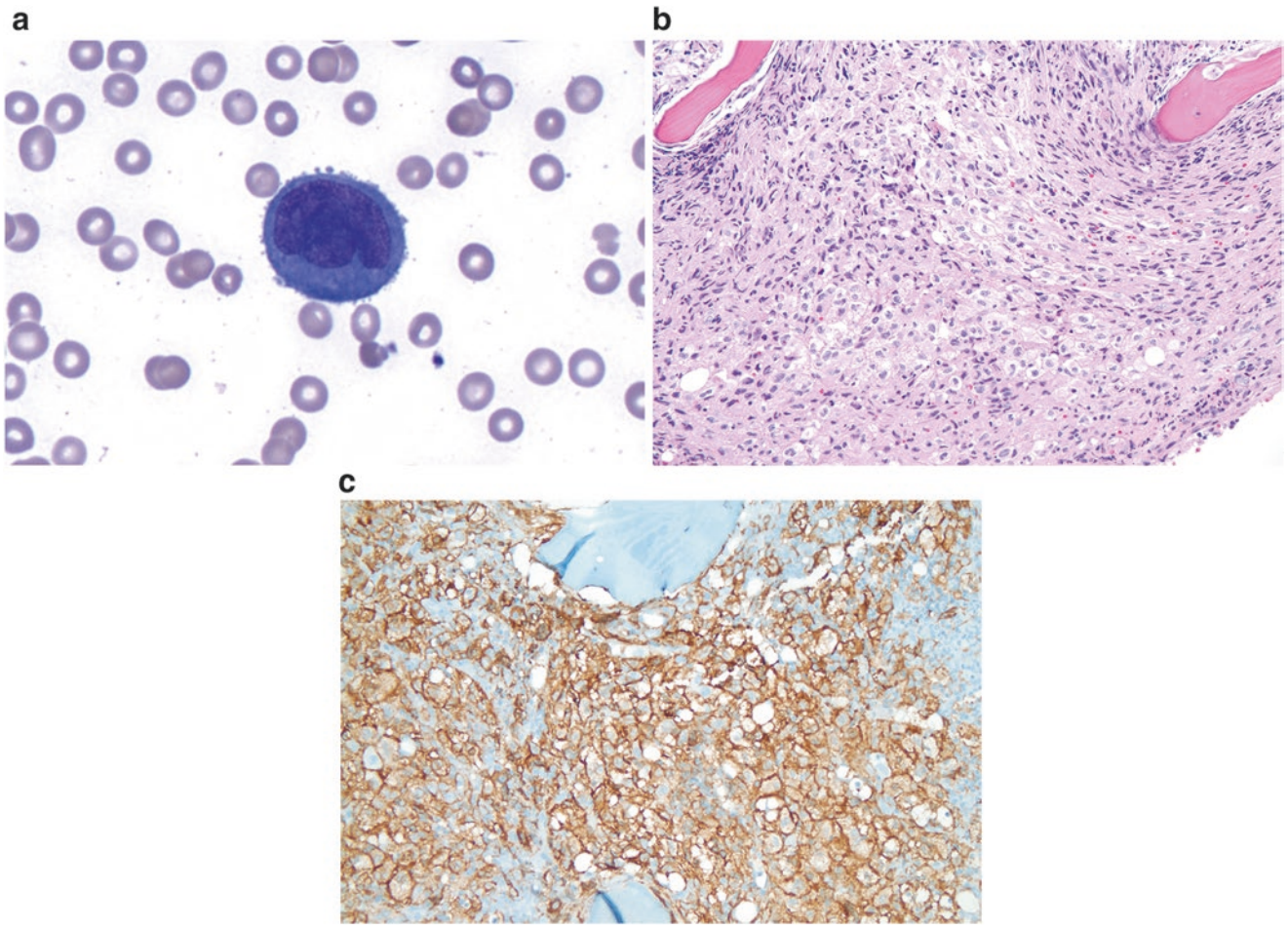

Fig. 14.4 Histiocytic sarcoma. (**a**) This hemodilute aspirate smear contains a large histiocytic cell with abundant basophilic cytoplasm and an enlarged and convoluted nucleus. (**b**) The bone marrow biopsy is effaced by an infiltrate of large cells with abundant eosinophilic cytoplasm and enlarged convoluted nuclei. A few bony trabeculae are present in the background; they are thinned with bony remodeling. (**c**) An immunohistochemical stain for CD163 highlights the neoplastic infiltrate with prominent membranous staining of the large cells, while sparing hematopoiesis in the upper right hand portion of the image

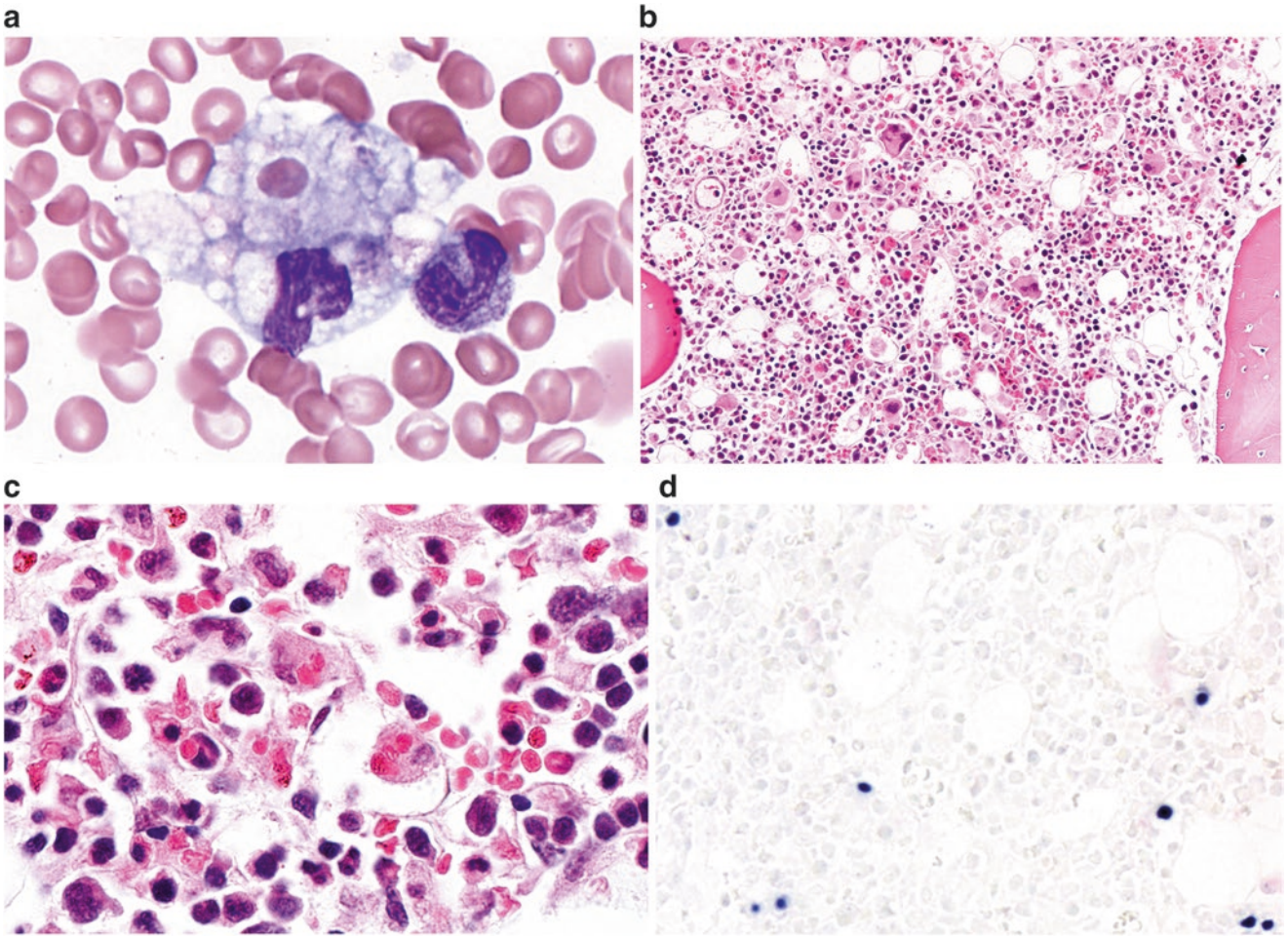

Fig. 14.5 Epstein-Barr virus (EBV)-associated hemophagocytic syndrome. This 14-month-old Hispanic boy presented with pancytopenia, elevated liver function tests, coagulopathy, hepatosplenomegaly, and a 2-week history of fever and a vasculitic rash. Ferritin was 8100 ng/L, LDH was 3168 U/L, soluble CD25 was elevated, and the EBV DNA load was 3723 copies/mL. Studies for cytomegalovirus (CMV), herpes simplex virus (HSV), parvovirus B19, respiratory viruses, and blood/urine/CSF cultures were all negative. No mutations were identified in *PRF1* or *MUNC13-4*, and there was no support for immune deficiency. (**a**) On a bone marrow aspirate smear, an activated histiocyte is present, engulfing an erythrocyte adjacent to a toxic band neutrophil. Hemophagocytosis was easy to find in the aspirate smear, and bare histiocytes were also present. (**b**) The bone marrow core biopsy at low power is mildly hypocellular for age, at 80% cellularity. A slight increase in megakaryocytes is present. Sinuses are dilated, and there are increased histiocytes showing erythrophagocytosis. (**c**) A higher-power image of the core biopsy demonstrates increased numbers of histiocytes within dilated sinuses, with prominent erythrophagocytosis. (**d**) In situ hybridization study for EBV-encoded small RNAs (EBERs) on the bone marrow biopsy highlights scattered lymphoid cells. The patient received antivirals and followed the HLH protocol for therapy. The complete blood cell count normalized, and subsequent bone marrows were normal. Of acquired hemophagocytic syndromes, approximately one third are due to infection. Viral infections outnumber other infections associated with acquired HLH, but virtually all infections have been associated. EBV is the most common virus among virus-induced hemophagocytic syndromes, and its prognosis is worse than for other viruses and acquired HLH

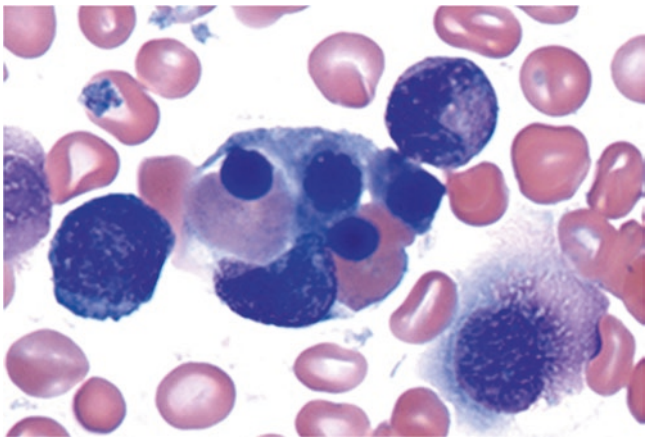

Fig. 14.6 Familial hemophagocytic lymphohistiocytosis. This 5-month-old presented with pancytopenia. A homozygous *RAB27A* mutation was found, and a diagnosis of Griscelli syndrome, an autosomal recessive syndrome, was made. The *RAB27A* gene is important in melanosome transport and proper function of cytotoxic T cells. Mutations in *RAB27A* result in hypopigmented skin and gray hair in infancy, typical of Griscelli syndrome, as well as recurrent infections and HLH. The bone marrow aspirate smear showed overt hemophagocytosis. Illustrated is a histiocyte with ingested erythroid precursors. An adjacent smudge cell is also present. Increased smudge cells are not uncommon when increased histiocytes are present. Familial or primary HLH is commonly due to inborn defects in lymphocytes that normally mediate control of infection and inflammatory conditions. These include a number of genetic disorders

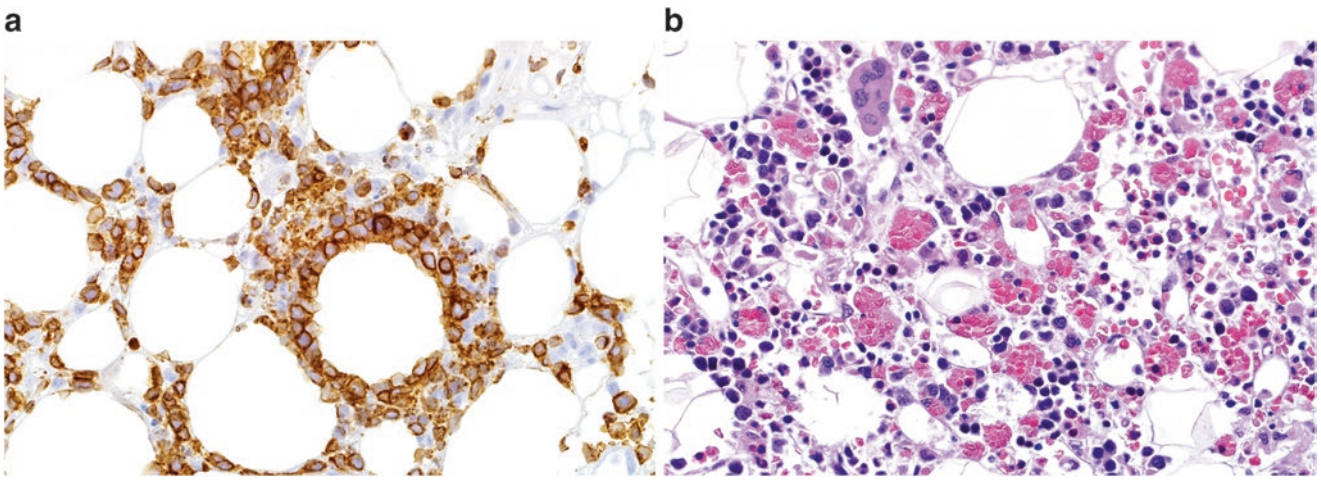

Fig. 14.7 Malignancy-associated hemophagocytic syndrome. Subcutaneous panniculitis-like T-cell lymphoma was diagnosed from a skin biopsy from the right upper arm of this 28-year-old woman. (**a**) High-power image of the subcutis highlights rimming of fat lobules by CD3-positive lymphoma cells. (**b**) There was no evidence of lymphoma in the bone marrow, but the patient met criteria for hemophagocytic syndrome. The bone marrow biopsy highlights numerous histiocytes stuffed with erythrocytes, showing a "bean bag" appearance on H&E-stained section

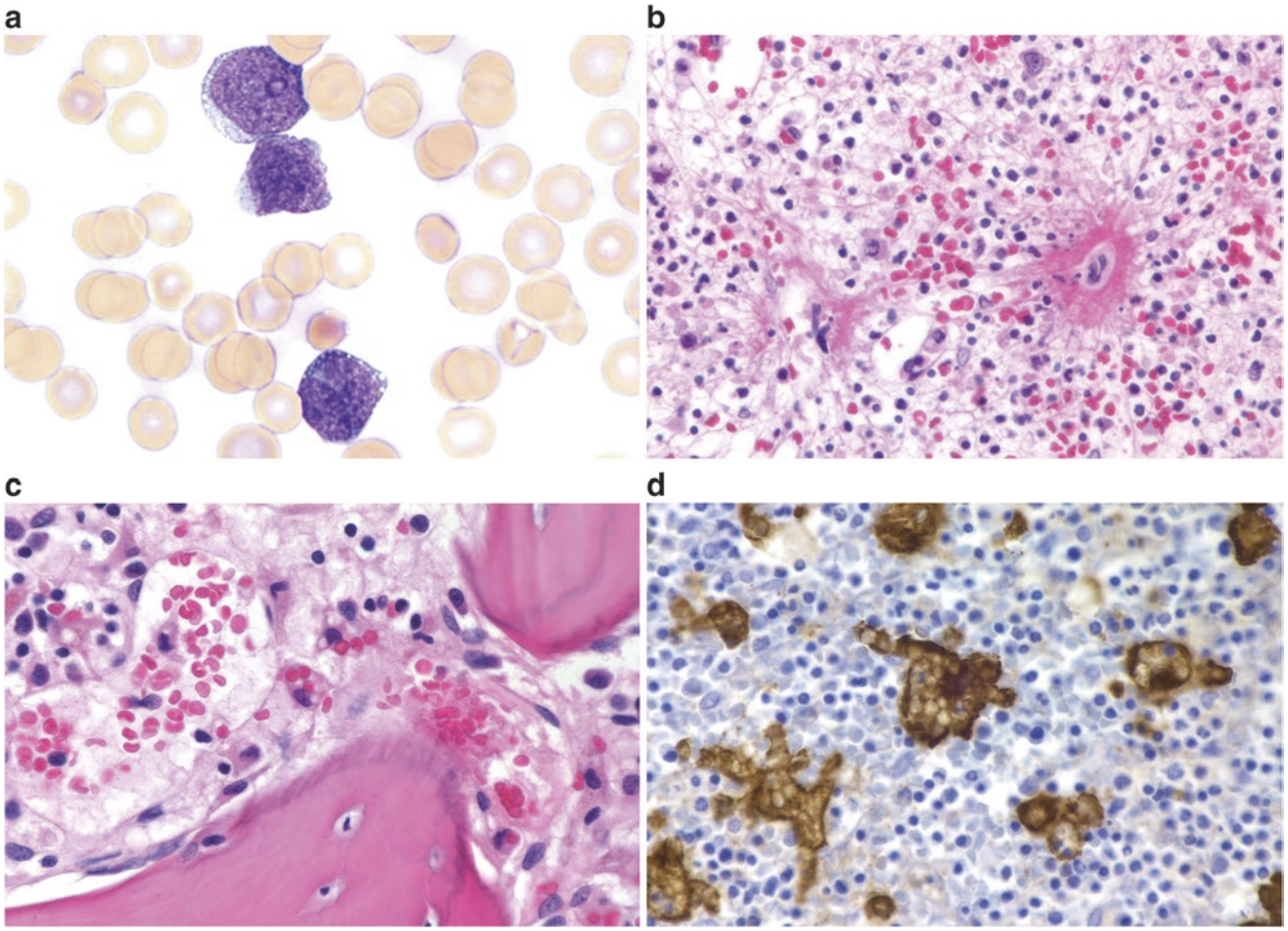

Fig. 14.8 Malignancy-associated hemophagocytic syndrome. This patient with acute lymphoblastic leukemia was found to have hemophagocytic syndrome at autopsy, with erythrophagocytosis found in the bone marrow, spleen, liver, and mesenteric lymph nodes. (**a**) Typical lymphoblasts are identified in the blood smear, with a high nuclear-to-cytoplasmic ratio, smooth chromatin, and a small amount of basophilic cytoplasm. (**b**) The bone marrow was hypocellular for the patient's age, with a prominence of stroma where the hematopoiesis has dropped out. A vessel at the right appears necrotic. (**c**) On higher power, the biopsy demonstrates dilated marrow sinuses containing bare histiocytes and histiocytes engulfing erythrocytes in the center of the image. (**d**) Immunohistochemical stain for CD163 can be quite useful to highlight histiocytes. Cell outlines can be seen within the cytoplasm of the CD163-positive histiocytes, helping to illustrate the phagocytosis of cells

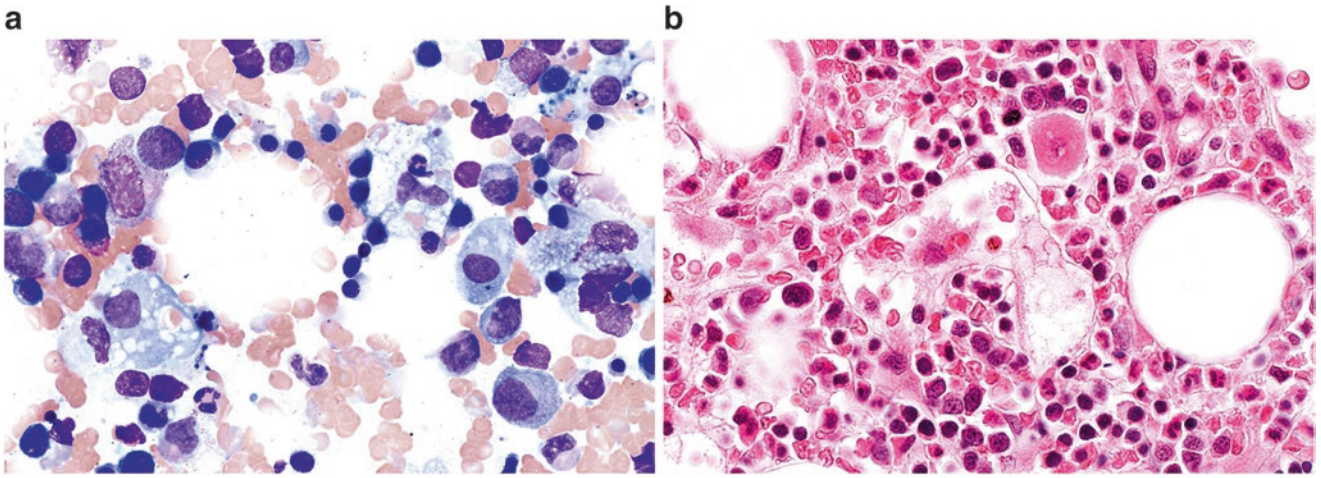

Fig. 14.9 Malignancy-associated hemophagocytic syndrome. Diffuse large B-cell lymphoma presenting as a retroperitoneal mass was diagnosed in this 76-year-old man. A staging bone marrow found no evidence of lymphoma, but the patient did have hemophagocytic syndrome. (**a**) Bone marrow aspirate demonstrates histiocytes containing erythrocytes and nucleated cells. (**b**) The trephine biopsy shows a dilated sinusoid in the middle of the image, with erythrophagocytosis

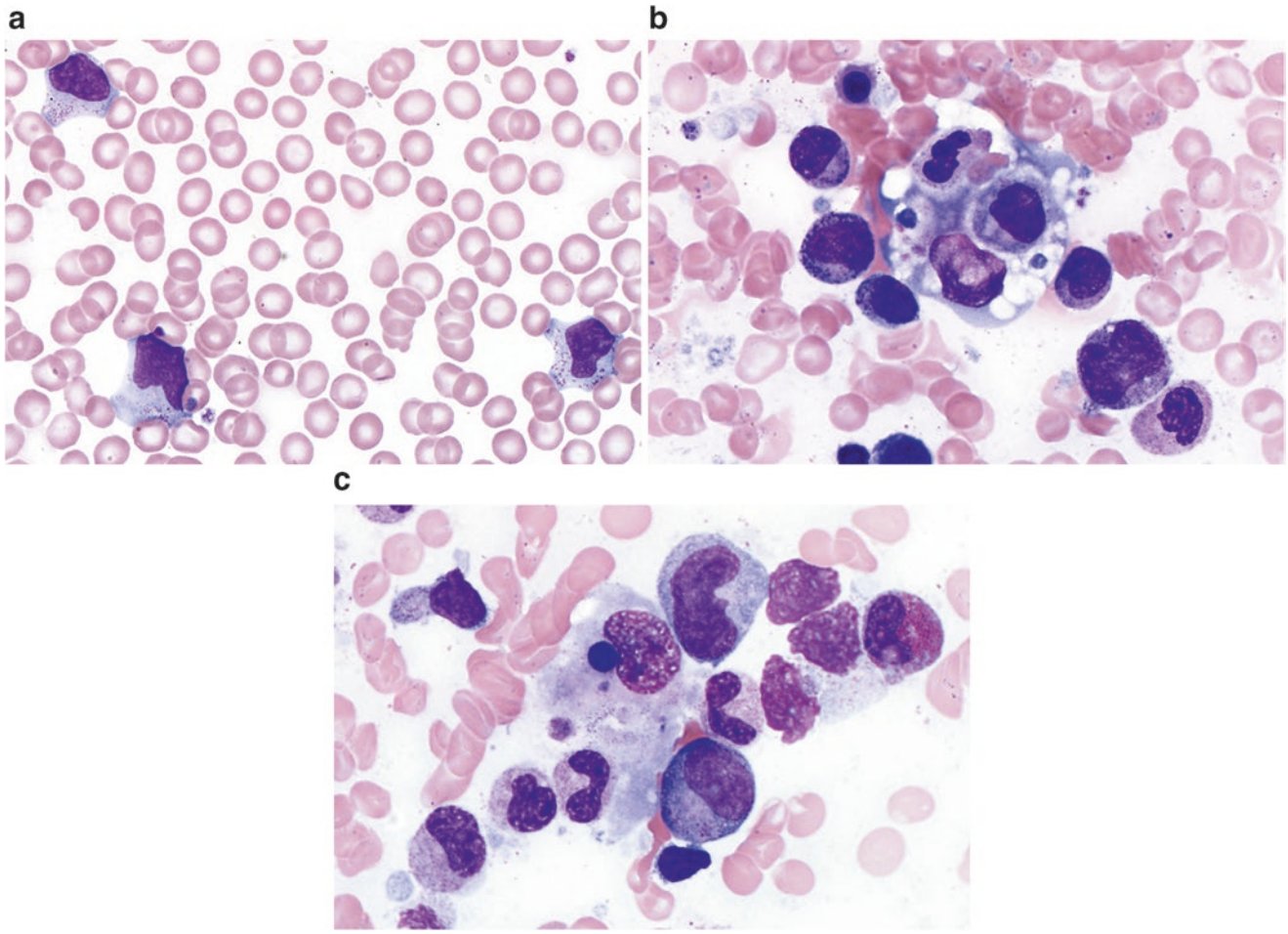

Fig. 14.10 Malignancy-associated hemophagocytic syndrome. This 12-year-old Native American girl presented with aggressive NK-cell leukemia and hemophagocytic syndrome. NK-cell and T-cell malignancies have a high association with hemophagocytic syndrome, but hemophagocytic syndrome has been reported with virtually all of the hematologic malignancies. (**a**) Here, the peripheral blood shows the "angry"-appearing large granular lymphocyte-like cells of aggressive NK-cell leukemia with abundant lightly basophilic cytoplasm containing large azurophilic granules. The nuclei are irregular with prominent nucleoli and partially condensed chromatin. (**b**) The bone marrow aspirate smear demonstrates phagocytosis of nucleated cells, including a leukemic cell at 2 o'clock. (**c**) In this image, a large neoplastic cell is adjacent to the histiocyte at 1 o'clock

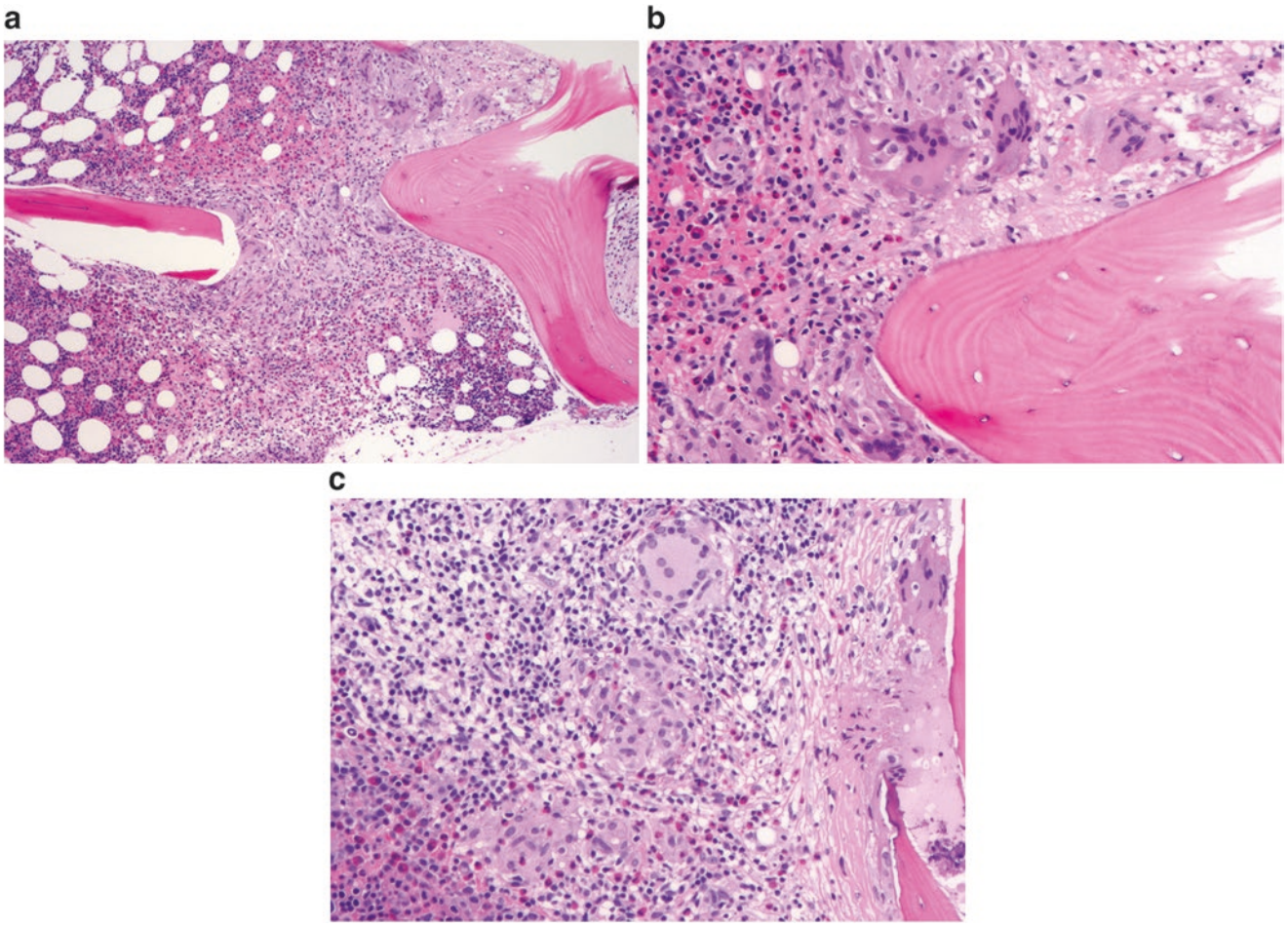

Fig. 14.11 Sarcoidosis. This 44-year-old woman presented with myalgias, arthralgias, anemia, and hypercalcemia. Imaging PET study showed a diffuse increased uptake within the bone marrow. A diagnosis of sarcoidosis was made after an infectious workup was negative; special stains for fungi and acid-fast bacilli were negative (*not shown*). (**a**) This bone marrow biopsy shows multifocal involvement by noncaseating granulomata with multiple multinucleated giant cells and eosinophilia surrounding the bone. Immunohistochemistry confirmed that the histiocytic cells were highlited by CD68 but were negative for S100 protein, langerin, and *BRAF*V600E (*not shown*). Interestingly, focal CD1a expression was noted. (**b**) On a higher-power view of the bone marrow biopsy, the bony trabeculae are rimmed by multinucleated giant cells. Bone marrow involvement in sarcoidosis is unusual, but it has been described in about 10% of cases [11]. These patients often present with cytopenias, hypercalcemia, and increased bony activity on PET scans. (**c**) In this image, the histiocytic infiltrate surrounding bone comprises histiocytes, lymphocytes, eosinophils, and multinucleated giant cells. At the top of the image, a Langhans giant cell is noted with nuclei arranged in a horseshoe-shaped pattern in the periphery of the cell; these multinucleated giant cells are formed by fusion of macrophages. Necrosis is absent. The differential diagnosis in this patient also included Langerhans cell histiocytosis, infection, and other immune disorders

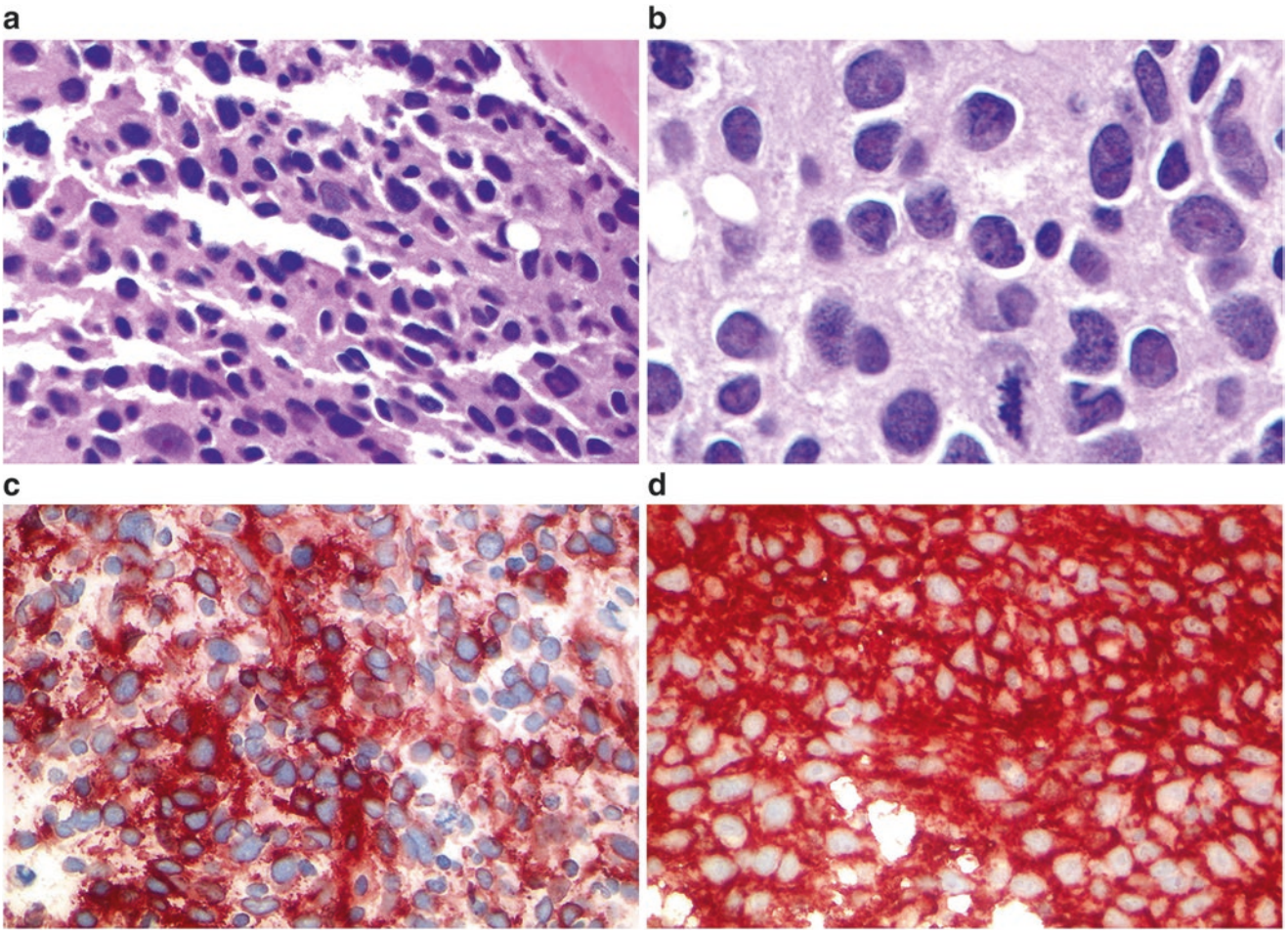

Fig. 14.12 Follicular dendritic cell sarcoma involving the bone marrow. (**a**) The H&E-stained bone marrow trephine section shows that the neoplastic cells extensively replace the normal bone marrow elements with ovoid tumor cells having indistinct cytoplasmic outlines. (**b**) Higher power shows large neoplastic cells with fine granular chromatin, distinct eosinophilic nucleoli, and a mitotic figure. (**c**) The neoplastic cells show membranous expression with an immunohistochemical stain for CD21, as well as strong and uniform membranous expression for CD23 (**d**) (*Courtesy of* Carlos Bueso-Ramos, MD)

Table 14.2 Comparison of histiocytic and dendritic neoplasms involving the bone marrow

	LCH	RDD	Histiocytic sarcoma	Reactive histiocytosis[a]
Hematologic findings	Leukocytosis	Leukocytosis	Cytopenias	May be abnormal depending on associated condition
	Elevated ESR	Elevated ESR		
		Polyclonal HG		
		Low albumin		
Distribution of histiocytes	Scattered and clusters	Sinusoidal	Clusters and sheets	Sinusoidal
Eosinophils	+	–	–	+/–
Emperipolesis	–	+	–	–
CD1a	+	–	–	–
S100	+	+	–	–
CD68	+	+	+	+
CD163	+/–	+	+/–	+
Langerin	+	–	–	–
BRAF V600E	+ (50%)	–	–	–

ESR erythrocyte sedimentation rate, *HG* hypergammaglobulinemia, *LCH* Langerhans cell histiocytosis, *RDD* Rosai-Dorfman disease
[a]Reactive histiocytosis includes hemophagocytic lymphohistiocytosis, sarcoidosis, and histiocytes associated with infection, inflammation, or accompanying malignancy

Table 14.3 Diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH)[a]

Molecular diagnosis consistent with HLH[d]
Or any five of the following eight criteria
1. Fever
2. Splenomegaly
3. Cytopenia affecting at least two lineages
Hemoglobin[b] <9 g/dL
Platelet count <100 × 10^9/L
Absolute neutrophil count <1 × 10^9/L
4. Hypertriglyceridemia (>3 mmol/L) and/or hypofibrinogenemia (<1.5 g/L)
5. Hemophagocytosis (bone marrow, spleen, lymph node)
6. Low to absent NK-cell activity
7. Elevated ferritin[c] (≥500 ng/mL)
8. Elevated soluble CD25 (≥2400 U/mL)

[a]Diagnostic criteria for hemophagocytic lymphohistiocytosis used in the HLH-2004 trial [9]
[b]In infants <4 weeks old, hemoglobin <10 g/dL is used
[c]Though extremely high ferritin levels (≥10,000 μg/L) correlate with HLH, this is not specific; high ferritin levels are reported with malignancy and iron overload [13]
[d]Mutations in a number of different genes have been described with HLH. These include but are not limited to *AP3B1*, *BLOC1S6*, *CD27*, *ITK, LYST*, *MAGT1*, *PRF1*, *RAB27A*, *SH2D1A*, *SLC7A7*, *STX11*, *STXBP1*, *UNC13D(MUNC13-4*), and *XIAP(BIRC4)*

Table 14.4 Classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis[a]

Febrile patient with known/suspected systemic juvenile idiopathic arthritis and ferritin >684 ng/mL
And any two of the following
1. Platelet count ≤181 × 10^9/L
2. Aspartate aminotransferase >48 U/L
3. Triglycerides >156 mg/dL
4. Fibrinogen ≤360 mg/dL

Adapted from Ravelli et al. [11]
[a]Laboratory abnormalities should not be due to other comorbid conditions

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