Cutaneous Myelomonocytic Infiltrates

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Introduction

Although extremely rare, myelomonocytic infiltrates can be found on the skin. Distinguishing different types is important since these infiltrates vary from benign to malignant in nature. Myelomonocytic skin lesions may be the first signs of a systemic disease amenable to systemic therapy or may be localized lesions that can be controlled with skin-directed therapy (Haniffa et al. 2006). Clinical features, cytomorphology, and immunophenotype are all important facets helpful in differentiating these disorders. In this chapter, the different myelomonocytic cutaneous infiltrates including cutaneous extramedullary hematopoiesis, cutaneous myelomonocytic infiltrates in patients with myelodysplastic syndrome (MDS)/myeloproliferative disorders (MPD), myeloid sarcoma, blastic plasmacytoid dendritic cell neoplasm (BPDCN), dendritic cell infiltrates, and histiocytic infiltrates are reviewed in detail. Table 16.1 highlights the cutaneous findings and epidemiology of the different myelomonocytic subtypes, and Table 16.2 outlines the immunophenotypical findings.

Cutaneous Extramedullary Hematopoiesis

Extramedullary hematopoiesis (EMH) is a common finding among patients with myeloid malignancies and hemoglobinopathies (Korsten et al. 1970; Glew et al. 1973; Rice et al. 1980; Lewkow and Shah 1984; Gowitt and Zaatari 1985; Gumbs et al. 1987; Shih et al. 1988; de Morais et al. 1996; Dibbern et al. 1997) or due to compromise of normal marrow space from foreign cells, cytokine-driven myeloid expansion, or stromal fibrosis (O'Malley 2007).

Definition

Cutaneous extramedullary hematopoiesis (CEMH) is defined as involvement of the skin with precursor hematopoietic tissue, which is normally in the bone marrow. The usual EMH sites include the liver and spleen, but almost all anatomical body locations can be affected including the skin (Koch et al. 2003; Pitcock et al. 1962; Mizoguchi et al. 1990). EMH is essential in fetal life, but after birth it is usually considered an

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Table 16.1 Cutaneous signs, epidemiological, and pattern of infiltration of cutaneous myelomonocytic infiltrates

Type of infiltrate	Cutaneous findings	Epidemiology	Pattern of infiltration
Extramedullary hematopoiesis	Pink, red, or bluish plaques, papules, or nodules	Most common with myelofibrosis	Perivascular and limited to dermis
Myeloid sarcoma	Papules, plaques, and nodules usually on the upper body	Male predominance, median age of 56 years	Dermis and subcutaneous tissue
Blastic plasmacytoid dendritic cell neoplasm (BPDCN)	Brown to violaceous nodules, plaques, or bruises	Male predominance, mean age of 61 years	Diffuse monomorphous infiltrate of medium-sized blast cells
Interdigitating dendritic cell sarcoma (IDCS)	Asymptomatic nodular lesions	Male predominance, median age 56.5 years	Dermis, spares epidermis
Follicular dendritic cell sarcoma (FDCS)	Subcutaneous nodules, can have paraneoplastic pemphigus	Mean age of 44 years Associated with Castleman disease and EBV	Dermis, can extend to subcutaneous or muscle but spares the epidermis
Langerhans cell histiocytosis (LCH)	Can resemble seborrheic dermatitis. Reddish-brown nodules or papules, rarely tumors	Male predominance	Dermis, often with epidermotropism
Dermal dendrocytic infiltrates	Well-circumscribed atrophic and wrinkled patch on the skin	Usually found in infancy or in childhood	Dermis, has epidermal atrophy
Indeterminate dendritic cell infiltrates	Solitary or multiple maculopapular or papulo-nodular lesions	Associated with low-grade B lymphomas	Dermis and can extend into subcutaneous fat

Table 16.2 Immunophenotypical markers of myelomonocytic cutaneous infiltrates

Marker	Myeloid sarcoma	Blastic plasmacytoid dendritic cell neoplasm	Interdigitating dendritic cell sarcoma	Follicular dendritic cell sarcoma	Langerhans cell histiocytosis	Dermal dendrocytic infiltrates	Indeterminate dendritic cell infiltrates
CD1a	–	–	–	–	++	–	+
CD4	+/–	+	+	+	+	+/–	+
CD21	–	–	–	++	–	–	–
CD34	++	–	–	–	–	++	–
CD35	–	–	–	++	–	–	–
CD45	++/–	+/–	+/–	–/wk+	+	–	+
CD68	+	+	+	+/–	+/–	+/–	+/–
CD123	–	++	–	–	–	–	–
Factor XIIa	–	–	–	–	–	++	–
Fascin	–	–	++	++	+	–	+
Lysozyme	+	–	+/–	–	+/–	–	+
S100	–	–	++	–/+	++	–	++
TCL1	–	++	–	–	–	–	–
Birbeck granules	–	–	–	–	++	–	–

Expression: ++ high, + present, +/– low or varies, – not present

abnormality (Koch et al. 2003). In a series of 510 patients with EMH, there were 27 patients (5.3 %) who were diagnosed with nonhepatosplenic EMH, and out of these, two patients had cutaneous EMH (Koch et al. 2003).

Epidemiology

The most common underlying condition associated with EMH is primary myelofibrosis. Little is known about the exact etiology of CEMH because

of its rarity, with most information coming from case reports or small series. Large series from three reports of 220 patients with myelofibrosis reported only one with CEMH (Bouroncle and Doan 1962; Pitcock et al. 1962; Ward and Block 1971). Literature documentation of CEMH comprises a total of about 30 cases and appears to be most frequently associated with myelofibrosis or myeloproliferative disorders (Patel et al. 1995; Revenga et al. 2000; Fernandez Acenero et al. 2003). Increased levels of transforming growth factor-beta appear to be associated with CEMH in patients with idiopathic myelofibrosis (Collie et al. 2013; Corella et al. 2008; Haniffa et al. 2006; Kawakami et al. 2008; Kwon et al. 1999; Lane et al. 2002; Miyata et al. 2008; Mizoguchi et al. 1990; Pagerols et al. 1998; Rodriguez et al. 1991; Rogalski et al. 2002; Ruberto et al. 1995).

Clinical Appearance of Cutaneous Lesions

Lesions presented as firm nodules in dermis and subcutaneous tissue. Pink, reddish, or bluish plaques, papules, or nodules are commonly seen and hemorrhage can develop around the lesion (Mizoguchi et al. 1990).

Pattern of Infiltration

Infiltrates are perivascular and may be limited to the dermis and subcutaneous tissue without epidermotropism.

Cytomorphology

Hematopoietic cells of different lineages and admixture could be seen. These include myeloid precursor cells in several stages of maturation, nucleated erythroid precursors, and mature megakaryocytes (Haniffa et al. 2006) (see Fig. 16.1). The presence of pure myeloid or erythroid precursors is rare, and in those cases with immature cells or blasts, a diagnosis of myeloid sarcoma should be ruled out (Mizoguchi et al. 1990).

Clinical Behavior

The prognosis in patients with nonhepatosplenic EMH is based on the underlying etiology. Hence, finding a cutaneous EMH should prompt a process for finding a systemic cause or even performing a bone marrow biopsy and a hematology consult. As a group, nonhepatosplenic EMH have

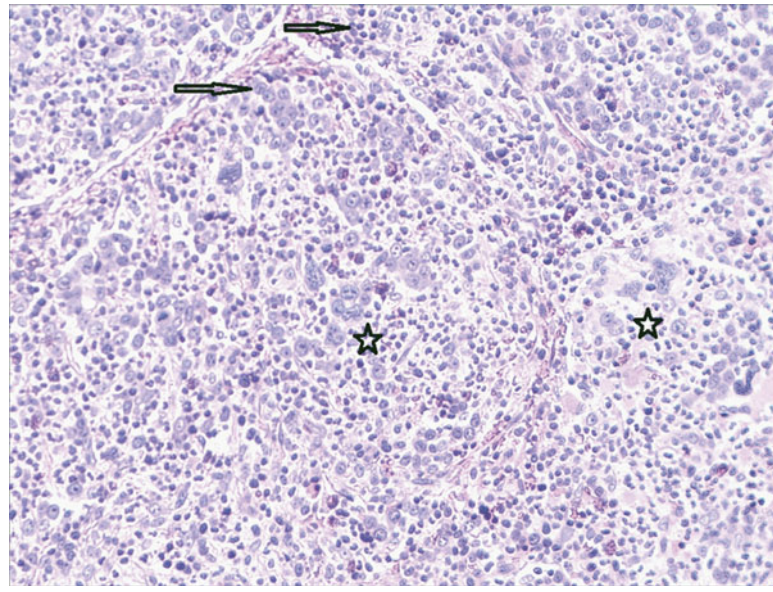

Fig 16.1 Extramedullary myeloid infiltrate in a child post-chemotherapy, (*arrows*) point to immature erythroid precursors and (*stars*) note the multinucleated megakaryocytes

poor outcome with the median survival of 13 months (Koch et al. 2003). Treatment is based on treating the underlying disorder, most commonly primary myelofibrosis.

Differential Diagnosis

CEMH is a type of infiltrative process in the "cutis" and is seen in patients with an underlying marrow disorder or even acute leukemia, and a bone marrow biopsy should be done in patients with isolated CEMH. Myeloid sarcoma with differentiated cells can also mimic CEMH, and immunohistochemistry for myeloid-monocytic markers such as CD43, lysozyme, CD68, and stem cell markers CD34 or CD117 may separate the immature from mature extramedullary hematopoiesis (Porcu et al. 1999). In general, a CD3-negative and CD43-positive immature single-field dermal infiltrate suggests a myeloid sarcoma instead of T-cell lymphoma.

Cutaneous Myelomonocytic Infiltrate in Patients with MDS/MPD

Introduction

Common myelomonocytic infiltrations under the generic nonspecific term "leukemia cutis" and more specifically myeloid sarcoma have been observed in patients with cutaneous lesions (List et al. 1991). Patients with an underlying myeloid disorder can develop specific (clonal, malignant) or nonspecific (reactive, benign) cutaneous lesions (Bluefarb and Webster 1953; Wong et al. 1995). Lesions that are specific are those in which the skin is involved by myelomonocytic leukemic cells and show histological changes compatible with leukemia cutis (LC). Nonspecific lesions include leukemoid reactions that may be due to bacterial, viral, and fungal infections secondary to immunosuppression or a hemorrhagic diathesis resulting in petechiae or purpura (Wong et al. 1995). Another subset of patients can developed neutrophilic infiltrates of the skin such as seen in pyoderma gangrenosum, bullous pyoderma, and Sweet's syndrome (Burton 1980) (see Chap. 15 *for discussion on pyoderma gangrenosum and Sweet's syndrome*). This chapter focuses the discussion on LC.

Definition

Cutaneous infiltrates that have similar histopathologic findings to the clonal underlying hematopoietic disorder are characterized as leukemia cutis (LC). LC is a clinical term applied to tumors in skin associated with underlying primary bone marrow neoplasms which could include mature and immature leukemia such as chronic lymphocytic leukemia, precursor lymphoblastic/leukemia, and acute to chronic myelomonocytic leukemia (Su 1994; Kumar 1997; Burns et al. 2005; Kaune et al. 2009; Lee et al. 2010; Wagner et al. 2012). LC discussion in this section is limited to those infiltrates that are histopathologically of myelomonocytic in origin.

Epidemiology

LC has been well described in patients with acute myelogenous leukemia but has rarely been associated with MDS or MPD. In one series of 44 cases of LC, 41 cases were related to myeloid leukemia and 2 to MDS, and 1 was related to polycythemia vera (Wong et al. 1995).

Clinical Appearance of Cutaneous Lesions

Lesions can be located anywhere on the body and can appear as either solitary or multiple purpuric papules or plaques. They can also be ulcerated or non-ulcerated nodules or subcutaneous masses. The most common anatomical location is the lower extremities, followed by the upper extremities, back, trunk, and face (Paydas and Zorludemir 2000).

Pattern of Infiltration

Dense and diffuse cellular infiltrate occupying the dermis and extending into the subcutaneous tissue is seen (Wong et al. 1995). In 18 of 44 cases of nonlymphocytic leukemias (mostly acute myeloid leukemia, two MDS, and a polycythemia vera), sparing of the grenz zone was observed. Infiltration of the nerves as well as the hair follicles, sebaceous glands, sweat glands, and vessels with a prominent "Indian filing"; perivascular targetoid pattern; or single-cell filing pattern of immature blast forms was also seen. Some infiltrates also involved exclusively the subcutaneous fat. Less common patterns include kaposiform-like and neutrophilic infiltrates with scattered blasts (8 of 52 cases), and atypical immature myeloid cells with a predominately perivascular pattern with associated MDS (Wong et al. 1995).

Cytomorphology

Morphology is similar to the primary myeloid neoplasm and shows dysplastic cells in those with an underlying myelodysplastic syndrome or myeloproliferative syndrome. At higher power, these cells can show variable cytological differentiation and marked pleomorphism and can stain positive for chloroacetate esterase or Leder stain if myelomonocytic in origin. Periodic acid-Schiff (PAS) stains most lymphoblasts in a dot pattern.

Depending on tumor cell differentiation, a blastic (undifferentiated) or maturing (differentiated) morphology could be seen. Blastic pattern shows monomorphous infiltrate of blasts. Neoplastic, neutrophilic, or eosinophilic precursors could be seen in differentiated forms (see Fig. 16.2a). Round myeloblasts admixed with myelocytes with nuclear folds are the rule in acute myeloid leukemia and in chronic myeloid leukemia (CML) and other myeloproliferative/MDS disorders. The morphologic hallmark is a maturing leukemic cellular pattern of myeloblasts, eosinophilic myelocytes, bands, and neutrophils that mimic the marrow appearance of CML. In acute monocytic leukemia, deeply folded grooved or kidney-shaped vesicular nuclei, positive for nonspecific esterase but negative for Leder stain, are the typical picture.

Immunophenotype

Immunophenotypical markers corresponding to the primary underlying myeloid neoplasm are observed. Most myeloid sarcoma should stain with CD43, lysozyme, and myeloperoxidase (MPO). MPO staining may be absent in monocytic LC (Cho-Vega et al. 2008).

Cytogenetic/Molecular Findings

LC is seen commonly in patients with acute myeloid leukemia with trisomy of chromosome 8 (Sen et al. 2000; Agis et al. 2002; Pileri et al. 2007). Tetrasomy and pentasomy of chromosome 8 have been reported as well (Ferrara et al. 1996; Gould et al. 2000).

Clinical Behavior

Patients with LC follow a clinical course similar to that of the underlying disease.

Differential Diagnosis

Myeloid sarcoma and Langerhans cell histiocytosis should be ruled out in patients with LC. Myeloid sarcoma can present as a type of leukemia cutis but can be differentiated from mature lymphocytic and lymphoblastic forms based on morphology, clinical history, and immunohistochemical profiling (see text on myeloid sarcoma). Most precursor B lymphoblasts should stain with CD79a, TDT, or CD10 with precursor T blast staining with cytoplasmic CD3 instead. Mature lymphocytic leukemia will mark with corresponding markers for chronic lymphocytic leukemia/lymphoma (CLL): CD23, CD5, and CD20 (see Fig. 16.2b).

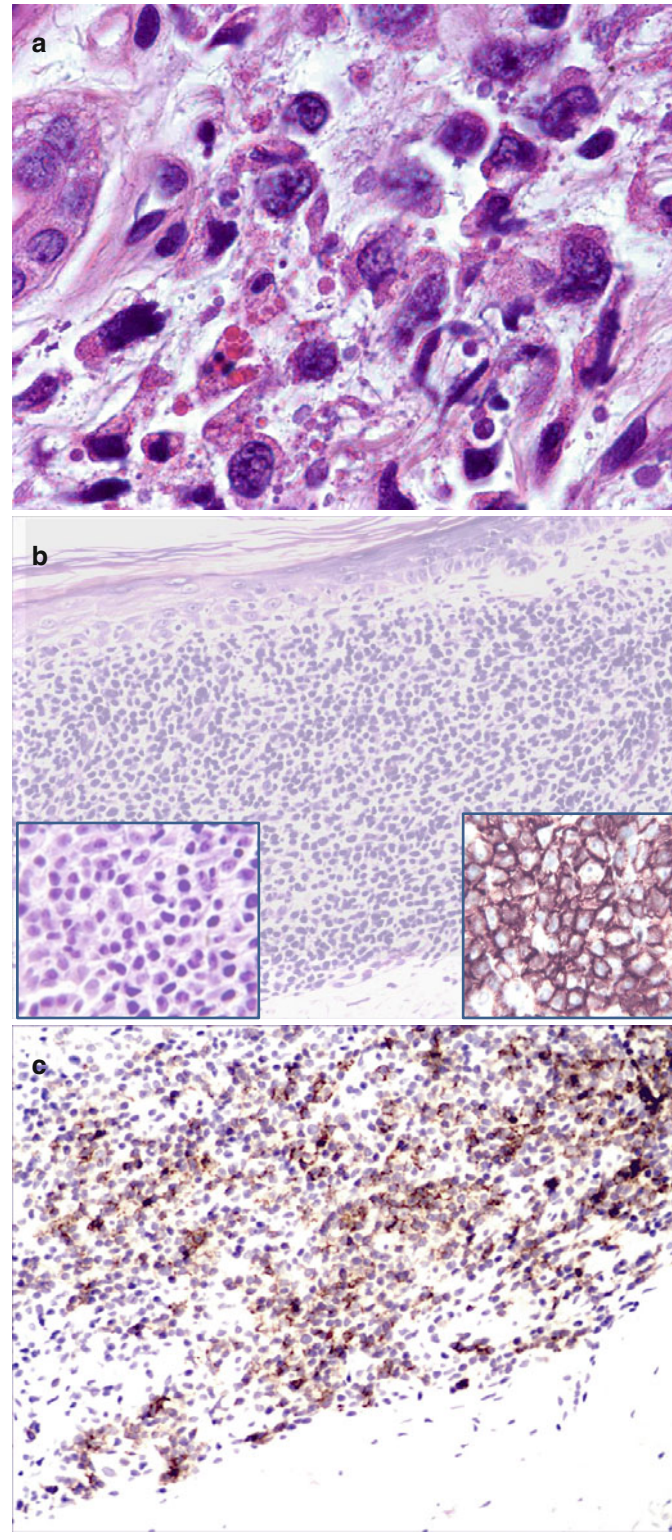

Fig. 16.2 (**a**) Myeloid sarcoma from a patient with a myeloproliferative neoplasm with eosinophilic differentiation. Note the cytoplasmic eosinophilic granules in some dysplastic eosinophils and immature cells. (**b**) Chronic lymphocytic leukemia/lymphoma involving skin with prolymphocytes (*inset*) CD20 (*inset2*) CD5 and (**c**) CD23 positivity

Myeloid or Granulocytic Sarcoma

The skin is one of the most common sites of involvement of myeloid sarcoma (MS). The mechanism by which myeloid blasts migrate to the skin is poorly understood, but it may be due to the expression of chemokine receptors and adhesion molecules by the blasts and the various cell types residing in the skin (Cho-Vega et al. 2008).

Definition

A myeloid sarcoma is by definition a tumor mass that is composed of myeloid blasts with or without maturation occurring at any anatomical site other than the bone marrow and resulting in an effacement of underlying tissue architecture. The lesion was first described by Burns in 1811 (Burns 1811). In 1853 the term "chloroma" was given to the lesion because such tumors often display a greenish color that fades on exposure to air due to the presence of myeloperoxidase (King 1853). MS is also known as a granulocytic sarcoma, chloroma, or extramedullary myeloid cell tumor (Rappaport 1966). MS is included in the 2008 WHO classification of myeloid neoplasm as distinct manifestation of acute myeloid leukemia (Swerdlow et al.2008). Patients with known myeloid leukemia infiltrates of any site of the body by myeloid blasts are not classified as MS unless the tumor effaces the tissue architecture. Skin, lymph node, gastrointestinal tract, bone, soft tissue, and testis are the most frequently affected sites (Falini et al. 2007; Pileri et al. 2007). Rarely, multiple anatomical sites are affected in a single patient.

Epidemiology

MS has been reported in 2.5–9.1 % of patients with AML and can occur concomitantly, following, or prior to systemic bone marrow leukemia (Wiernik and Serpick 1970; Liu et al. 1973; Krause 1979; Neiman et al. 1981). Males are more affected than females with a ratio of 1.2:1. Median age is 56 years but is also seen in older patients (Falini et al. 2007; Pileri et al. 2007; Hurley et al. 2013). In one series of 61 biopsied cases, 13 had skin involvement (Neiman et al. 1981). Incidence of MS after allogeneic hematopoietic cell transplantation has been reported to be 0.2–1.3 % with poor overall survival (Bekassy et al. 1996; Szomor et al. 1997).

Clinical Appearance of Cutaneous Lesions

Multiple skin lesions such as papules, plaques, and/or nodules are commonly described. The torso is more commonly involved, but one study did favor the involvement of the upper body (Hurley et al. 2013).

Pattern of Infiltration

Pleomorphic blasts are seen in the dermis and subcutaneous tissue.

Cytomorphology

Blasts are identifiable by their immature cytomorphology with dispersed nuclear chromatin with nucleoli and abundant mitotic activity with scattered apoptotic cells (Liu et al. 1973; Krause 1979; Neiman et al. 1981; Eshghabadi et al. 1986; Meis et al. 1986). Eosinophilic myelocytes can also been seen (Lin et al. 1990). Myelomonocytic or pure monoblastic morphology can be seen (Falini et al. 2007; Pileri et al. 2007) (see Fig. 16.3).

Immunophenotype

CD68/KP1 is the most commonly expressed marker followed by MPO, CD117, CD99, lysozyme, CD34, TdT, CD56, CD61, CD30, and CD4 (Pileri et al. 2007). In one series lysozyme was positive in all cases, with myeloperoxidase in 56 %, CD68 in 100 %, and CD34 in 19 % of patients (Hurley et al. 2013). Cases can

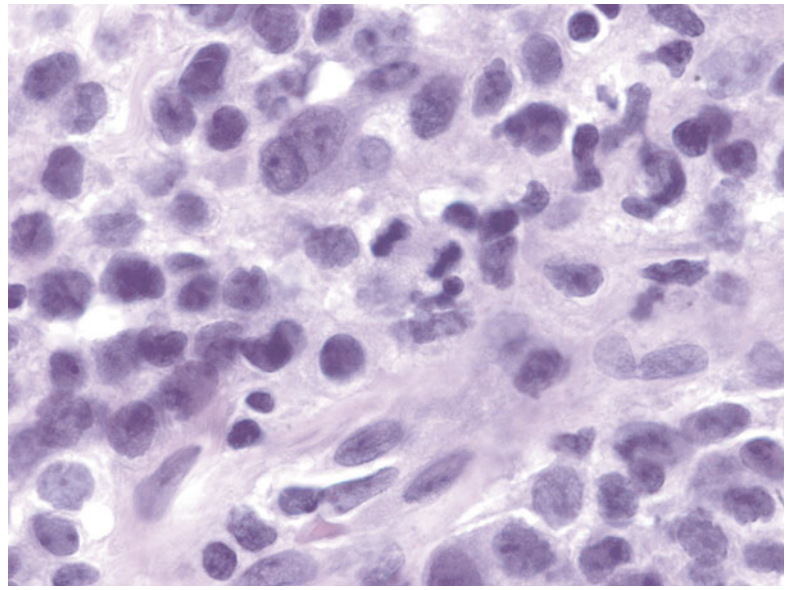

Fig. 16.3 Myeloid sarcoma without differentiation (blastic form). Note the atypical blasts with open vesicular and dispersed chromatin

demonstrate aberrant expression of T- or B-cell lineages which can lead to an erroneous diagnosis (Hanson et al. 1993).

Cytogenetic/Molecular Findings

Chromosomal aberrations by FISH or cytogenetics are detectable in 55 % of cases (Pileri et al. 2007). Monosomy 7; *MLL* (myeloid/lymphoid or mixed-lineage leukemia) rearrangement; trisomy 4; monosomy 16, 16q, 5q, and 20q; and trisomy 11 are some of the reported abnormalities (Pileri et al. 2007). Trisomy of chromosome 8 and inversion 16 are more common in MS involving the skin (Dachary et al. 1986; Cronin et al. 2009; Hurley et al. 2013). *NPM1* mutations are seen in 16 % of cases (Falini et al. 2005, 2007).

Clinical Behavior

Prognosis is poor in patients with MS. MS is considered an equivalent of a diagnosis of acute myeloid leukemia and should be treated with induction chemotherapy (Eshghabadi et al. 1986; Lin et al. 1990). Allogeneic hematopoietic cell transplantation carries a higher probability of prolonged survival or cure (Breccia et al. 2004; Pileri et al. 2007). Radiation therapy can be useful in emergency or palliative settings (Bakst et al. 2012).

Differential Diagnosis

T- and B-cell malignancies especially non-Hodgkin lymphoma can be differentiated by cytomorphology and immunohistochemistry (46 % of cases in one series) (Byrd et al. 1995). Lymphoblastic leukemia, melanoma, Ewing's sarcoma, blastic plasmacytoid dendritic cell neoplasm (see section on BPDCN below), and immature EMH should be considered as well (Ngu et al. 2001).

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

Definition

BPDCN is an aggressive tumor derived from the precursors of plasmacytoid dendritic cells. BPDCNs have myeloid ancestors in common with monocytes and are found in the bone marrow and skin (Liu et al. 2009). BPDCN was previously

known as blastic NK-cell lymphoma, CD4 + CD56+ hematodermic neoplasm, and plasmacytic dendritic cell leukemia, making it difficult to track historically (Lim et al. 2013). Cutaneous findings are seen universally in BPDCN and 50 % of patients present with isolated cutaneous lesions (Cota et al. 2010).

Epidemiology

BPDCN is a very rare neoplasm representing approximately 0.8 % of the primary cutaneous lymphomas (Petrella and Facchetti 2010). There is a 3.3:1 male/female ratio with most patients being elderly with a mean age at diagnosis of 61 years. Though it usually occurs in the elderly, it can occur in children and has been reported in patients as young as 8 years of age (Lim et al. 2013). There is no increased incidence in any one ethnic group (Feuillard et al. 2002; Jacob et al. 2003; Herling and Jones 2007).

Clinical Appearance of Cutaneous Lesions

Patients usually present with asymptomatic brownish to violaceous nodules, plaques, or bruise-like areas which can be solitary or in multiple locations on the skin (Feuillard et al. 2002; Julia et al. 2013; Lim et al. 2013). In one study 73 % of patients had nodular lesions only and 12 % had bruise-like patches, while 15 % had disseminated and mixed lesions (Julia et al. 2013). Twenty percent of patients will have regional lymphadenopathy (Lim et al. 2013).

Pattern of Infiltration

BPDCN is characterized by a diffuse, monomorphous infiltrate of medium-sized blast cells with irregular nuclei, fine chromatin, and one to several small nucleoli. Tumor cells occupy the dermis and spare the epidermis but will eventually invade the subcutaneous fat (Petrella et al. 1999, 2005; Cota et al. 2010).

Cytomorphology

A plasmacytoid cytological appearance is seen in medium- to high-power view, but these cells usually lack a perinuclear hof of true plasma cells (see Fig. 16.4). The cells are derived from plasmacytoid dendritic cells, an antigen presenting cell, resident in skin and lymph nodes. Cytoplasm is usually scant to moderate, may be eccentric, and appears gray blue and agranular on Giemsa stain. Mitoses are rarely prominent and angioinvasion is rare. BPDCN is negative with nonspecific esterase and myeloperoxidase cytochemical stains.

Immunophenotype

BPDCN cells are positive for CD4, CD56, CD123, and TCL1 (Tecchio et al. 2009; Cota et al. 2010). Rarely CD56 can be negative, but if CD4, CD123, and TCL1 are present, this does not exclude the diagnosis. Occasionally CD7, CD33, CD43, CD45RA, TL1-A, and HLA-DR can be positive. Most tumors lack conventional myeloid and lymphoid T- and B-cell antigens (Petrella et al. 1999, 2002; Herling et al. 2003; Petrella et al. 2004, 2005; Reichard et al. 2005; Willemze et al. 2005; Assaf et al. 2007; Herling and Jones 2007; Pilichowska et al. 2007; Garnache-Ottou et al. 2009). Newer markers that can be diagnostic include CD2AP (Marafioti et al. 2008), BDCA-2 (CD303), and BDCA-4 (CD304) (Garnache-Ottou et al. 2009). CD68 is expressed in 50 % of cases as small cytoplasmic dots (Petrella et al. 2004, 2005).

Cytogenetic/Molecular Findings

Cytogenetic analysis often shows a complex karyotype (Feuillard et al. 2002; Petrella et al. 2005; Herling and Jones 2007; Ascani et al. 2008; Garnache-Ottou et al. 2009) or deletions of tumor suppressor genes in the majority of cases (Jardin et al. 2009). Genomic losses affecting 5q21 or 5q34, 12p13, 13q21, 6q23, 15q, and chromosome 9 have been reported (Petrella et al.

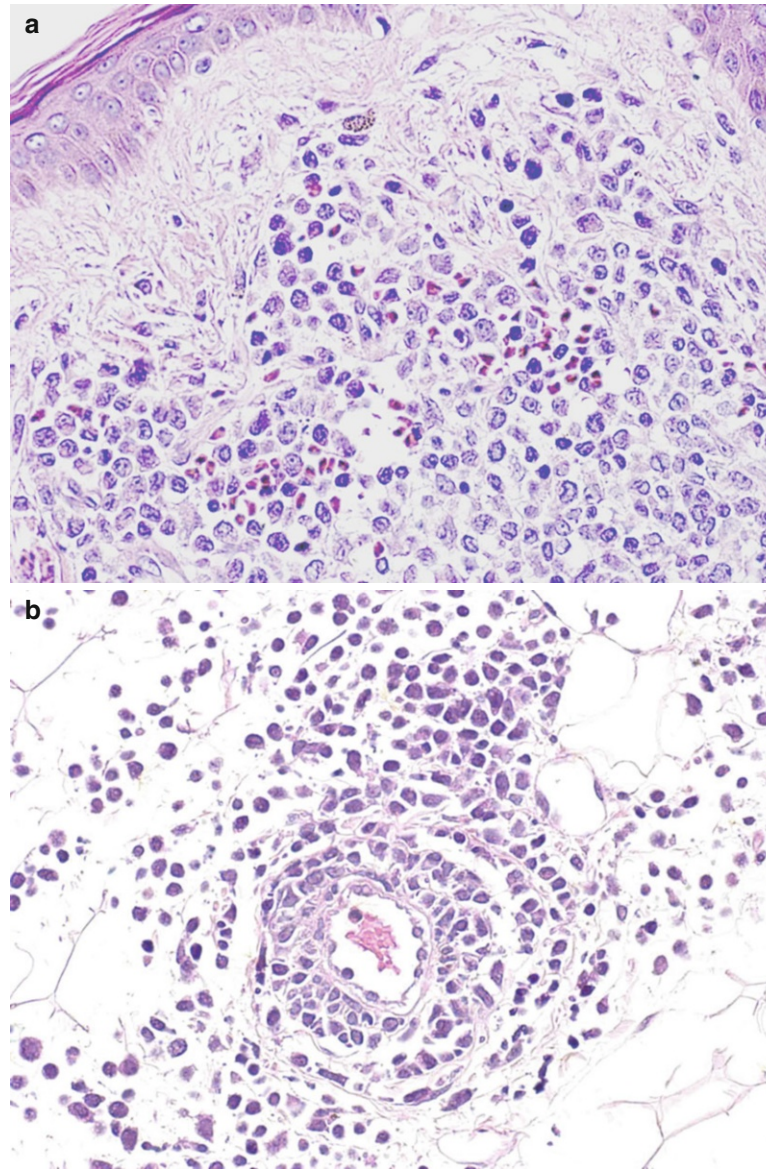

Fig. 16.4 Blastic plasmacytoid dendritic cell leukemia involving the skin. (**a**) Subepidermal plasmacytoid blasts with single-cell pattern. (**b**) Targetoid perivascular pattern

1999; Leroux et al. 2002; Reichard et al. 2005; Guo et al. 2011; Lucioni et al. 2011; Julia et al. 2013). A recent study suggested that a mutation of *CDKN2A*/*CDKN2B* on chromosome 9 could help identify more aggressive cases (Lucioni et al. 2011). One study showed that IgH and TCR-gamma gene rearrangement analysis done in 34 biopsies from 27 patients showed a polyclonal smear in all cases (Cota et al. 2010).

Clinical Behavior

The majority of patients present with asymptomatic solitary or multiple skin lesions usually with nodules and plaques. Low-level bone marrow involvement is often seen at presentation or soon after (Feuillard et al. 2002; Herling and Jones 2007; Ascani et al. 2008; Garnache-Ottou et al. 2009). Leukemic dissemination is part of the

natural progression of the disease and can be present before, at the same time with, or after skin lesions (Julia et al. 2013). In one series 61 % of patients had bone marrow, lymph node, and/or blood involvement (Julia et al. 2013). Lymphadenopathy and/or splenomegaly are common. Overall prognosis is poor with medial overall survival duration of 12–14 months (Feuillard et al. 2002; Lim et al. 2013). Increased age predicts a worse prognosis. Patients with skin involvement only have initially less aggressive course and can benefit from skin-directed therapy or steroids (Pileri et al. 2012). This approach is especially useful in older patients or younger patients with multiple comorbidities who are not eligible for systemic intensive chemotherapy or allogeneic stem cell transplant. Treatment with radiation therapy and chemotherapy has been used with varying success in patients with BPDCN. Radiation therapy can achieve a complete response in 80 % of patients with localized disease but is associated with a short time to relapse, with a mean of 5.5 months (Dalle et al. 2010). Combined chemotherapy regimens have been given with varying success including cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP-like), or cytarabine-based treatments. Complete responses have been documented in 50–75 % of patients, but relapses usually occur within months and chemotherapy resistance develops (Ng et al. 2006; Dalle et al. 2010). Recently, the incorporation of L-asparaginase in chemotherapy regimen showed promising results (Gruson et al. 2013). Skin findings are almost always present at relapse. In elderly patients who are not a candidate for systemic therapy, skin lesions can respond to monotherapy with steroids. Allogeneic stem cell transplantation is the only known curative approach with mean survival of 31 months. It should be considered in younger patients who achieve complete remission with induction chemotherapy (Reimer et al. 2003; Dalle et al. 2010).

Differential Diagnosis

Skin localizations of myelomonocytic disorders and MS would have overlapping immunohistologic findings, but a CD56, CD4, and CD123 positive blastic skin leukemic infiltrate with plasmacytoid cytomorphology would favor a BPDCN. Extranodal natural killer/T-cell nasal-type tumors and PTCL-unspecified and pleomorphic T-cell lymphomas can be ruled out with immunohistochemistry and cytomorphology with EBV + favoring extranodal NK cell and T cells that are CD30- and CD68-negative T-cell infiltrate, favoring the two latter entities (Petrella et al. 2005).

Interdigitating Dendritic Cell Sarcoma (IDCS)

Definition

Interdigitating dendritic cells present antigens to T cells and regulate cellular immune response (Steinman et al. 1997; Imai et al. 1998; Steinman 2003; Chung et al. 2004; Maeda et al. 2005; Saygin et al. 2013). These cells originate from hematopoietic precursors through the conversion of Langerhans cells as they travel to the lymph node and from the differentiation of myeloid and lymphoid precursor cells (Wood et al. 1985; Rosenzweig et al. 1996; Steinman et al. 1997; Wu and Liu 2007; Saygin et al. 2013). IDCS is a malignant disorder of interdigitating dendritic cells.

Epidemiology

IDCS is an extremely rare disease and skin involvement has rarely been reported. In a large pooled analysis of a total of 462 cases of dendritic cell sarcomas, there were 100 cases of IDCS with seven having skin findings (Saygin et al. 2013). Median age at diagnosis in this pooled analysis was 56.5 years (range 21 months to 88 years) with an M/F ratio of 1.38:1 (Saygin et al. 2013). A clonal relationship between IDCS and low-grade B-cell lymphomas has been reported in patients with both diseases (Feldman et al. 2008; Fraser et al. 2009; Shao et al. 2011). IDCS has been reported following

the use of calcineurin inhibitors, and this may be due to their effect by dampening the responses of T cells to which IDCs present antigens (Gordon et al. 2007; Wu et al. 2010; Saygin et al. 2013).

Clinical Appearance of Cutaneous Lesions

Most lesions are asymptomatic and are nodular in nature. Nodules can be erythematous or brownish but not ulcerative. These lesions can occur anywhere and can appear in crops (Hui et al. 1987; Lee et al. 2009).

Pattern of Infiltration

IDCS usually is found throughout the dermis but spares the epidermis. The tumor can invade the subcutaneous tissue and can be seen in a fascicular pattern forming intertwining bundles (Hui et al. 1987; Lee et al. 2009).

Cytomorphology

Large spindle to ovoid cells are seen forming whorls. Cells have coarse nuclear chromatin with moderate to abundant cytoplasm resembling histiocytes albeit with indistinct borders (Ylagan et al. 2003). Small lymphocytes intermingling with the large histiocytic cell population is a key diagnostic feature that is less typical of carcinomas and sarcomas (Ylagan et al. 2003). In one series lymphoplasmacytic infiltration was seen in 63 % of tumors and rarely epithelioid cells were seen (7 %) (Saygin et al. 2013).

Immunophenotype

Cells are S100 positive and CD45 positive and have variable CD68 positivity (Gaertner et al. 2001; Pileri et al. 2002). Some IDCS are vimentin, HLA-DR, and fascin positive (Maeda et al. 2005). Lysozyme can also be positive (Gaertner et al. 2001). CD21 and CD35 will be negative (Ylagan et al. 2003). B-cell markers such as CD20 and T-cell markers such as CD3 and CD5 are usually negative. Cytokeratin, myeloperoxidase, CD1a, CD21, CD23, CD30, CD35, CD21, CD34, CD79a, BCL-2, and BCL-6 should all be negative (Gaertner et al. 2001; Pileri et al. 2002, 2007; Jiang et al. 2013). ATPase can be strongly positive in some cases (Turner et al. 1984; Fonseca et al. 1998). Birbeck granules are not seen on ultrastructure examination (Gaertner et al. 2001; Pileri et al. 2002).

Cytogenetic/Molecular Findings

Immunoglobulin and T-cell receptor genes are in a germ line configuration (Weiss et al. 1990).

Clinical Behavior

Prognosis is poor in cases of disseminated disease, and about half the patients will die of their disease. In the pooled analysis of 100 cases of IDCS, the median survival for patients with metastatic disease was 9 months, but cases with local disease did not reach median and 2-year survival rates (Saygin et al. 2013). In patients with localized disease, there was no difference in the overall survival between surgery and nonsurgical modalities such as radiation therapy (Saygin et al. 2013). In the metastatic setting, combined chemotherapy such as CHOP, ICE, and ABVD was most commonly used in patients with IDCS (Saygin et al. 2013). In metastatic IDCS, there was a statistical trend ($P=0.1$) toward improved overall survival in those patients who received surgery, and these authors recommended surgery with adjuvant chemotherapy (Saygin et al. 2013).

Differential Diagnosis

Inflammatory pseudotumors typically show no histological atypia and are seen in patients with fever and other constitutional symptoms. Hodgkin lymphoma, which is remarkably rare in skin, and non-Hodgkin lymphoma may be considered if fibrosis is present inducing a pseudospindle morphology (Jayaram and Abdul Rahman 1997; Fonseca et al. 1998; Mohanty et al. 2003; Pillay et al. 2004). Langerhans cell sarcomas and other sarcomas such as peripheral nerve sheath tumors should be ruled out (Ylagan et al. 2003). Intranodal myofibroblastoma, true histiocytic lymphomas, melanomas, and anaplastic large-cell lymphomas are also considerations if spindle and anaplastic pattern is prominent (Fonseca et al. 1998).

Follicular Dendritic Cell Sarcoma (FDCS)

Definition

Follicular dendritic cells (FDC) present and retain antigens for B cells and stimulate B-cell proliferation and differentiation while having complex interactions with T cells (Tew et al. 1990; Wu et al. 1996; Fonseca et al. 1998). They are of mesenchymal origin. FDCS is a malignant expansion of FDC. FDCS usually presents as lymphadenopathy in the majority of cases but can present in a wide variety of extra nodal sites including the skin. In a large pooled analysis including 462 cases, 343 had FDCS and two of these had skin findings (Saygin et al. 2013).

Epidemiology

There is a wide age range with an adult predominance and a mean age of 44 years (Pileri et al. 2002; Nguyen et al. 2005). There is a female predominance for the inflammatory pseudotumor variant (Cheuk et al. 2001; Pileri et al. 2002; Vargas et al. 2002). FDCS can occur in association with Castleman disease usually in the hyaline vascular type (Chan et al. 1994). The inflammatory pseudotumor-like variant is associated with Epstein-Barr virus (EBV) (Arber et al. 1998). There may be an association between FDCS and autoimmunity with paraneoplastic pemphigus and myasthenia gravis seen in cases of FDCS (Lee et al. 1999; Wang et al. 2005; Meijs et al. 2008; Saygin et al. 2013).

Clinical Appearance of Cutaneous Lesions

Lesions can appear as subcutaneous nodules (Kazakov et al. 2005). In patients with FDCS, a paraneoplastic pemphigus can also occur and resembles ulcerations on the skin or mucosal surfaces, erythematous patches, or lichen planus.

Pattern of Infiltration

FDCS invading the tissue presents as spindle-shaped infiltrates in the dermis that may extend into the subcutaneous or even muscle but spares the epidermis (Kazakov et al. 2005).

Cytomorphology

Spindled to ovoid cells forming fascicles, whorls, diffuse sheets, or nodules are characteristic. Individual cells generally show indistinct cell borders and a moderate amount of eosinophilic cytoplasm. Nuclei are oval or elongated and finely dispersed chromatin. Nuclear pseudoinclusions are common and binucleated and multinucleated tumor cells are seen (2008). On electron microscopy, the long cytoplasmic projections and desmosomal junctions are seen, while Birbeck granules and numerous lysosomes are not seen (Fonseca et al. 1998).

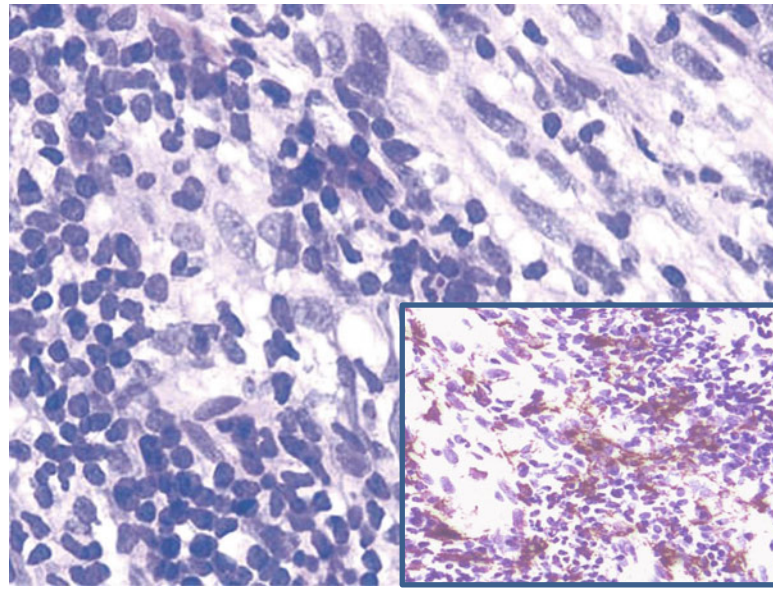

Fig. 16.5 Follicular dendritic cell sarcoma (FDCS) with CD21 + CD35+ (*inset*) histiocytes

Lymphoplasmacytic infiltration is frequently present in greater than 90 % of cases (Saygin et al. 2013). Rarely, Reed-Sternberg-like cells can lead to a mistaken diagnosis of Hodgkin disease (Mohanty et al. 2003) (see Fig. 16.5).

Immunophenotype

CD21, CD35, R4/23, Ki-FDC1p, and KiM4 are positive in FDCS (Chan et al. 1997; Fonseca et al. 1998; Ylagan et al. 2003). There is variable expression of CD68. Clusterin is strongly positive but is negative or weakly positive in other dendritic cell tumors (Grogg et al. 2004, 2005). Desmoplakin, vimentin, fascin, epidermal growth factor receptor (EGFR), CD45, and HLA-DR can be variable (Chan and Chan 1997; Fonseca et al. 1998; Sun et al. 2003; Ylagan et al. 2003).

Cytogenetic/Molecular Findings

Immunoglobulin and T-cell receptor genes are germ line configuration (Weiss et al. 1990). There is very limited data on genetic changes seen in patients with FDCS (Sander et al. 2007).

Clinical Behavior

Not much is known about skin-specific findings or clinical behavior because of the rarity of this disease in the skin. The most frequent location of lymphadenopathy is cervical and intra-abdominal and about half of patients will present with a local mass (Saygin et al. 2013). FDCS has a fairly benign course with median survival for local disease was 168 months (range 2–360 months). Risk of local recurrence and distant metastasis is around 27–28 % (Saygin et al. 2013). Larger tumor size (≥6 cm), presence of coagulative necrosis, high mitotic count (≥5 per 10 high-power fields), and cytological atypia are associated with poor prognosis (Chan et al. 1997; Shia et al. 2006; Saygin et al. 2013). Surgery is the mainstay of treatment for FDCS. Adjuvant therapy for fully resected patients is unclear. A pooled analysis showed no benefit of adjuvant radiation therapy (Saygin et al. 2013). This analysis did show that in the metastatic setting, treatment with combined adjuvant chemotherapy and radiotherapy ($n=23$) only resulted in two deaths due to disease showing the importance of adjuvant treatment in advanced FDCS. Regimens designed for the management of aggressive lymphomas such as

CHOP (cyclophosphamide, vincristine, doxorubicin, prednisone), ICE (ifosfamide, carboplatin, etoposide), and ABVD (adriamycin, bleomycin, vincristine, dacarbazine) have been tried with variable success (Saygin et al. 2013).

Differential Diagnosis

FDCS has the same differential diagnosis as IDCS. This includes ruling out inflammatory pseudotumors, histiocytic lymphomas, melanomas, Langerhans cell sarcomas, other sarcomas such as peripheral nerve sheath tumors (Ylagan et al. 2003), ALCL, IDCS, Hodgkin disease, intranodal myofibroblastoma, and NHL (Jayaram and Abdul Rahman 1997; Fonseca et al. 1998; Mohanty et al. 2003; Pillay et al. 2004).

Cutaneous Langerhans Cell Histiocytosis

Definition

Langerhans cell histiocytosis (LCH) represents a clonal accumulation of Langerhans cells that are a cutaneous antigen presenting cells (Newman et al. 2007). After being triggered by a new antigen, the LC migrates to the regional lymph nodes and activates antigen-specific T cells that return to the skin (Romani et al. 2003). Cutaneous lesions are present in one third of patients. In the Hashimoto-Pritzker disease, also known as congenital, self-healing reticulohistiocytosis, disease is limited to the skin and resolves rapidly over a period of weeks (Divaris et al. 1991). This is a rare disease and is more commonly seen in children than adults.

Epidemiology

Incidence is 5 per million populations per year with most cases occurring in childhood. There is a predilection for males (Pileri et al. 2002; Salotti et al. 2009). The WHO states that the disease is more common in northern European descent patients and rare in blacks (2008). LCH usually presents with either unifocal or multifocal bone disease or as a multisystem disease. LCH has been associated with Epstein-Barr virus, malaria, and leukemias (Newman et al. 2007). In a large series of 314 patients diagnosed between 1946 and 1996, the median age at diagnosis was 24.5 years (Howarth et al. 1999). Isolated skin findings were seen in 14 patients of this series. There are disease processes that include LCH. Letterer-Siwe disease usually presents in the first 2 years of life and is the acute disseminated form of LCH (Newman et al. 2007). Hand-Schuller-Christian disease is a chronic multisystem disease seen in older children and consists of the classic triad of bone disease, diabetes insipidus, and exophthalmos (Gianotti and Caputo 1985). Eosinophilic granuloma of bone is a common manifestation of LCH in adults. The most frequent anatomical sites of LCH in adults were the lung (62 %), bone (50 %), and skin (15 %). One-third of patients developed multiple organ involvement (Gotz and Fichter 2004).

In contrast to acute illness observed in children, LCH in adults has usually more chronic course.

Clinical Appearance of Cutaneous Lesions

Patients with Letterer-Siwe disease have extensive cutaneous lesions and classically resemble seborrheic dermatitis with involvement of the scalp, face, trunk, and perineum (Zachary and MacDonald 1983). Hand-Schuller-Christian disease has papulonodular, granulomatous, or seborrheic dermatitis-like lesions (Zachary and MacDonald 1983). In Hashimoto-Pritzker disease, lesions are seen at birth and are widespread reddish-brown nodules that regress (Divaris et al. 1991). LCH can also present with papules, pustules, vesicles, petechiae, or purpura (Zachary and MacDonald 1983; Stein et al. 2001; Park et al. 2012).

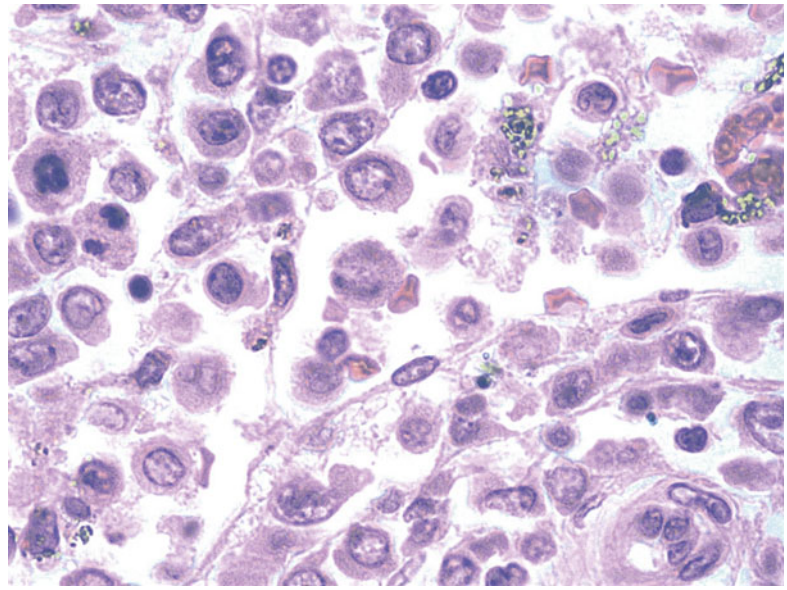

Fig. 16.6 Langerhans cell histiocytosis with eosinophilic neoplastic cells, some with grooved nuclei positive for CD1a and S100

Pattern of Infiltration

Dermal infiltrate of large epithelioid cells with abundant eosinophilic cytoplasm and indented or reniform nuclei (Hashimoto and Pritzker 1973).

Cytomorphology

Oval cells about 10–15 μm in size with grooved, folded, or indented or lobulated nuclei with fine chromatin are seen (2008) (WHO) (see Fig. 16.6). Placental alkaline phosphatase can be used in archival material to evaluate for LCH (Newman et al. 2007). Eosinophils are scattered throughout the infiltrate and the epidermis is free of infiltrating cells (Hashimoto and Pritzker 1973). Letterer-Siwe disease has infiltrates that are composed largely of LCs with scattered lymphocytes, eosinophils, and occasional neutrophils (Wells 1979). In Hand-Schuller-Christian disease, there is a prominent granulomatous reaction made of aggregates of histiocytes and rarely cells with xanthomatous changes (Altman and Winkelmann 1963). In Hand-Schuller-Christian disease, clusters of eosinophils are prominent and there are occasional multinucleated giant cells (Risdall et al. 1983). Birbeck granules which have a tennis racquet shape and zipper-like appearance are present in 0–40 % of cells by electron microscopy (Zunino-Goutorbe et al. 2008). An ultrastructural finding that has been proposed to be specific for congenital self-healing reticulohistiocytosis (CSHR) is the presence of concentrically laminated dense-core bodies in the same cells that contain Birbeck granules (Hashimoto et al. 1984).

Immunophenotype

LCH stain positive for S-100 protein, CD1a, CD45, and CD101. CD1a staining is specific for LCH (Newman et al. 2007). CD68 staining can be positive (Wheller et al. 2013). Langerin (CD207) is also specific for LCH (Chikwava and Jaffe 2004; Lau et al. 2008). Placental alkaline phosphatase can be used in archival material to evaluate for LCH (Newman et al. 2007). LCH do not express CD34 or MS-1 (a marker for dendritic perivascular macrophages that are found in non-LCD histiocytosis) (Goerdt et al. 1993).

Cytogenetics/Molecular Findings

LCH has been shown to be clonal by X-linked androgen receptor gene assay (HUMARA) (Willman et al. 1994; Yu et al. 1994; Yousem et al. 2001). No consistent molecular genetic defect has been identified (Murakami et al. 2002). Recently, recurrent BRAF V600E somatic mutation was identified in 35 of 61 patients (57 %) with LCH (Badalian-Very et al. 2010).

Clinical Behavior

Self-limited LCH should be distinguished from other forms of LCH because disseminated disease has a worse prognosis and requires an aggressive therapy such as chemotherapy. Thorough investigation and follow-up of patients with LCH should be performed because clinically, histopathologically, and immunohistochemically, one cannot determine those individuals with more aggressive disease (Kapur et al. 2007; Wheller et al. 2013). In self-limited disease, one group suggests a follow-up period of 2 years including laboratory tests and radiographs (abdominal ultrasound and chest x-ray (Zunino-Goutorbe et al. 2008). LCH can lead to diabetes insipidus due to infiltration and scarring in the hypothalamic pituitary area or due to an autoimmune process with antibodies to vasopressin (Dunger et al. 1989; Grois et al. 1995, 2006). The most important risk factor for developing DI in patients with LCH was multisystem disease (Grois et al. 2006). Self-limited disease of the skin can be treated with topical nitrogen mustard (Wong et al. 1986; Munn and Chu 1998; Stein et al. 2001), psoralen plus ultraviolet A (PUVA) phototherapy (Munn and Chu 1998; Stein et al. 2001), imiquimod (Taverna et al. 2006), excimer laser (Vogel et al. 2008), and radiation therapy (Lichtenwald et al. 1991). Though most patients are initially treated with corticosteroids, thalidomide (Imanaka et al. 2004; Park et al. 2012), and etoposide have the best results for patients with widespread cutaneous disease (Munn and Chu 1998; McClain 2005; McClain and Kozinetz 2007; Gadner et al. 2008; Park et al. 2012). Agents such as methotrexate, cyclophosphamide, cyclosporine, 6-mercaptopurine, and vinblastine have also been reported to work (McLelland et al. 1990; Munn and Chu 1998; Stockschlaeder and Sucker 2006; Park et al. 2012). Current treatment should be based on the Histiocyte Society evaluation and treatment guidelines with current recommendations for treatment of all categories, excluding single-system disease to be systemic therapy (Minkov et al. 2009; French Histiocytosis Society 1996). Currently, for systemic involvement, prednisone and vinblastine for 12 months are the recommended treatment (Gadner et al. 2008; Minkov et al. 2009; Gadner et al. 2013). One year of therapy was proven to decrease recurrence when compared to six cycles (Gadner et al. 2013). Progressive disease or recurrence should be treated with 2-chlorodeoxyadenosine and cytarabine (Bernard et al. 2005). Stem cell transplantation should be considered in these patients (Steiner et al. 2005). This disease can affect the skin or other organs. Recent case series has suggested that an inhibitor of mutated BRAF (vemurafenib) could be a novel promising targeted therapy for patients with LCH carrying V600E mutation (Haroche et al. 2013).

Differential Diagnosis

LCH can be mistaken for disorders that cause Langerhans cell hyperplasia such as scabies, contact dermatitis, indeterminate dendritic cell infiltrates, pityriasis lichenoides et varioliformis acuta, and different T-cell lymphoproliferative disorders such as lymphomatoid papulosis, mycosis fungoides, parapsoriasis, or cutaneous T-cell hyperplasia (Christie et al. 2006; Pigozzi et al. 2006; Bhattacharjee and Glusac 2007; Drut et al. 2010). Since it can involve the skeleton in adults, it can be confused for multiple myeloma (Malpas 1998).

Dermal Dendrocytic Infiltrates

Definition

Dermal dendrocytes encompass a double population of dermal-resident cells that include

CD34+ cells and factor XIIIa-positive cells. These two cell types have different resident sites and function (Sontheimer et al. 1989; Hoyo et al. 1993; Narvaez et al. 1996; Drut 2007). CD34 also labels dermal dendrocytes, with an overlapping immunoprofile with CD34 expression seen in cellular dermatofibroma. Lesions may harbor some cells expressing the alternative antigen though the majority do not (Goldblum and Tuthill 1997).

Epidemiology

Rare cases often mistaken for neurofibromas. Can present in infant and early childhood as hamartomas.

Clinical Appearance of Cutaneous Lesions

Well-circumscribed atrophic and wrinkled patch on the skin. These can look similar to a congenital melanocytic nevus or skin-colored papules (Cerio et al. 1989; Ohata and Kawahara 2002; Drut 2007).

Pattern of Infiltration

Dermal proliferation of fusiform cells. Epidermal atrophy can be seen.

Cytomorphology

Fusiform or spindle-shaped cells that are seen in the dermis. These can be arranged in several layers and around small vessels (Drut 2007).

Immunophenotype

The tumor cells are positive for CD34+ and factor XIIIa and are usually negative for S100 (Cerio et al. 1989; Hoyo et al. 1993; Narvaez et al. 1996; Goldblum and Tuthill 1997).

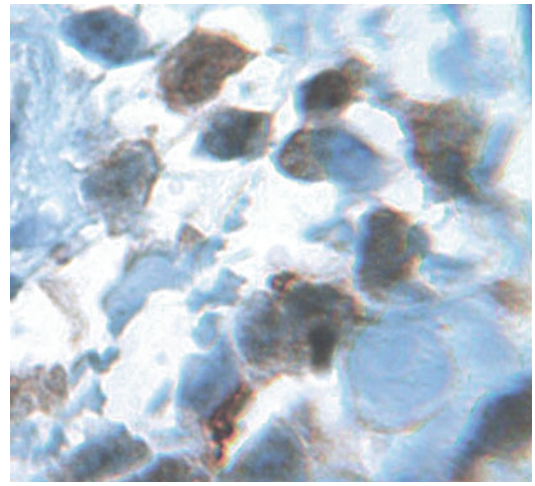

Fig. 16.7 Factor XIIIa positive dendrocytes

Clinical Behavior

These lesions are usually benign and do not require intensive treatment (see Fig. 16.7).

Differential Diagnosis

Neurofibroma, dermatofibrosarcoma protuberans, and giant-cell fibroblastoma should all be considered in the differential. Xanthomas and even indeterminate dendritic neoplasm can stain with Factox XIII and figures in the differential of immunstain results. Staining for factor XIIIa is the most sensitive test for dermal dendrocytic infiltrates (Cerio et al. 1989; Sontheimer et al. 1989; Gray et al. 1990; Hoyo et al. 1993; Narvaez et al. 1996; Goldblum and Tuthill 1997; Ohata and Kawahara 2002; Drut 2007).

Indeterminate Dendritic Cell Infiltrates

Definition

Indeterminate dendritic cell tumor, also known as indeterminate cell histiocytosis (ICH), is a neoplastic proliferation of normal dendritic

accessory cells, usually found in the dermis. These cells should lack intracytoplasmic Birbeck granules but share morphologic and immunophenotypical features with Langerhans cells (Ferran et al. 2007). Since Langerhans cells lose their Birbeck granules when cultured and since some indeterminate cells migrate to the epidermis and may become Langerhans cells, some authors speculate that indeterminate cells may represent a mature form of Langerhans cells (Chu et al. 1982; Romani et al. 1989; Teunissen et al. 1990; Weiss et al. 2005).

Epidemiology

Indeterminate dendritic cell tumor is a very rare disorder and may be associated with low-grade B-cell lymphoma (Vasef et al. 1995).

Clinical Appearance of Cutaneous Lesions

Solitary or multiple asymptomatic maculopapular or papulo-nodular lesions (Rosenberg and Morgan 2001; Ferran et al. 2007). Most lesions are located on the trunk, face, neck, or extremities. Rarely, generalized distribution has been reported (Sidoroff et al. 1996).

Pattern of Infiltration

A diffuse infiltrate comprising of cells with irregular nuclear grooves and clefts that resemble Langerhans cells. Infiltration is seen in the dermis but may extend into the subcutaneous fat. The epidermis is sparred (Rosenberg and Morgan 2001).

Cytomorphology

Cells resemble Langerhans cells with irregular nuclear grooves and clefts. Cytoplasm is abundant and eosinophilic. Multinucleated giant cells may be seen and there may be spindling of some cells. Cytoplasm is abundant and is eosinophilic. These cells lack Birbeck granules. Desmosomes are lacking but the cells can have interdigitating cell processes (2008).

Immunophenotype

Indeterminate cells usually express S-100 and CD1a antigens but always lack Birbeck granules on ultrastructural exam (Ferran et al. 2007). Desmosomes are lacking but there can be complex interdigitating cell processes. These cells are negative for specific B- and T-cell markers, CD30, CD163, CD21, CD23, and CD35. There is variable positivity for CD45, CD68, lysozyme, and CD4 (Vener et al. 2007) (see Fig. 16.8).

Cytogenetic/Molecular Findings

One case was shown to be clonal by human androgen receptor gene assay (Vener et al. 2007).

Clinical Behavior

Disease is usually limited to the skin and extra cutaneous lesions and systemic symptoms are rare (Ferran et al. 2007). Etiology of this disorder remains unknown, but it has been postulated that it can represent a reactive disorder secondary to antigenic exposure (Ratzinger et al. 2005). Proliferations of indeterminate cells have been seen in nodular scabies (Hashimoto et al. 2000) and in healed lesions of pityriasis rosea (Wollenberg et al. 2002).

Differential Diagnosis

The differential diagnosis is similar to that for LCH and includes LCH, scabies, pityriasis rosea, and T-cell lymphomas.

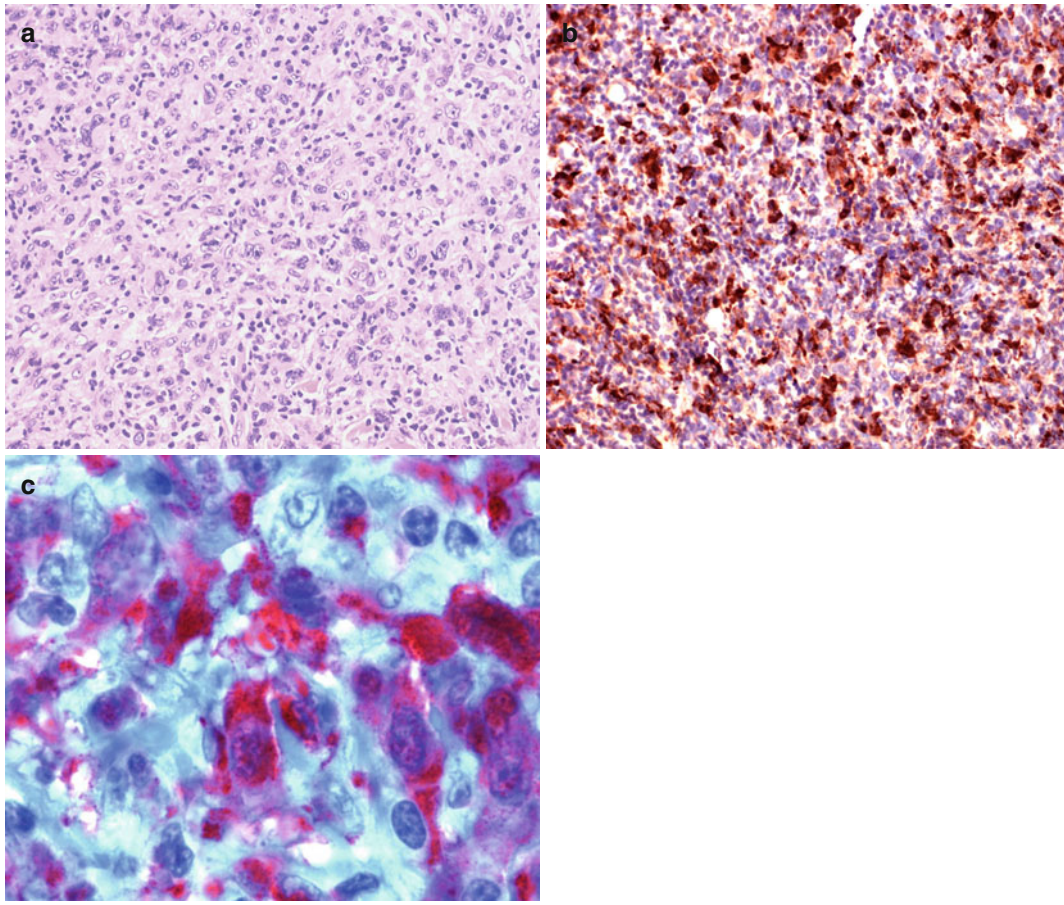

Fig. 16.8 (**a**) Indeterminate dendritic cell sarcoma. (**b**) CD68 stain. (**c**) S100 stain

Conclusions

The different myelomonocytic infiltrates can be associated with underlying systemic disorders such as EMH in patients with primary myelofibrosis or infiltrates related to MDS or AML or can be a primary disorder on their own. The broad differential diagnosis includes being able to differentiate myelomonocytic infiltrates into a specific subtype and also to exclude other similar causes such as precursor lymphoblastic leukemia (see Fig. 16.9) which may present with papulo-nodular tumors as with other myelomonocytic infiltrates but will have a different cytomorphology and immunophenotypical profile (CD10, Pax5, CD22 positive). Table 16.2 summarizes the different immunophenotypical markers that can be used to help differentiate between the different myelomonocytic infiltrates discussed above.

Differentiation of each disease entity relies on the use of clinical findings and careful evaluation of the cytomorphology and immunophenotypical profile including evaluation of atypical cells circulating in the peripheral blood (see Fig. 16.10).

Consensus on the treatment of these disorders continues to be difficult due to the rare nature of many of these diseases. Consortium group recommendations and when possible, clinical trials should be the mainstay of treatment decisions. Prognosis can be variable and further research is needed to use targeted therapy in these rare tumor subtypes.

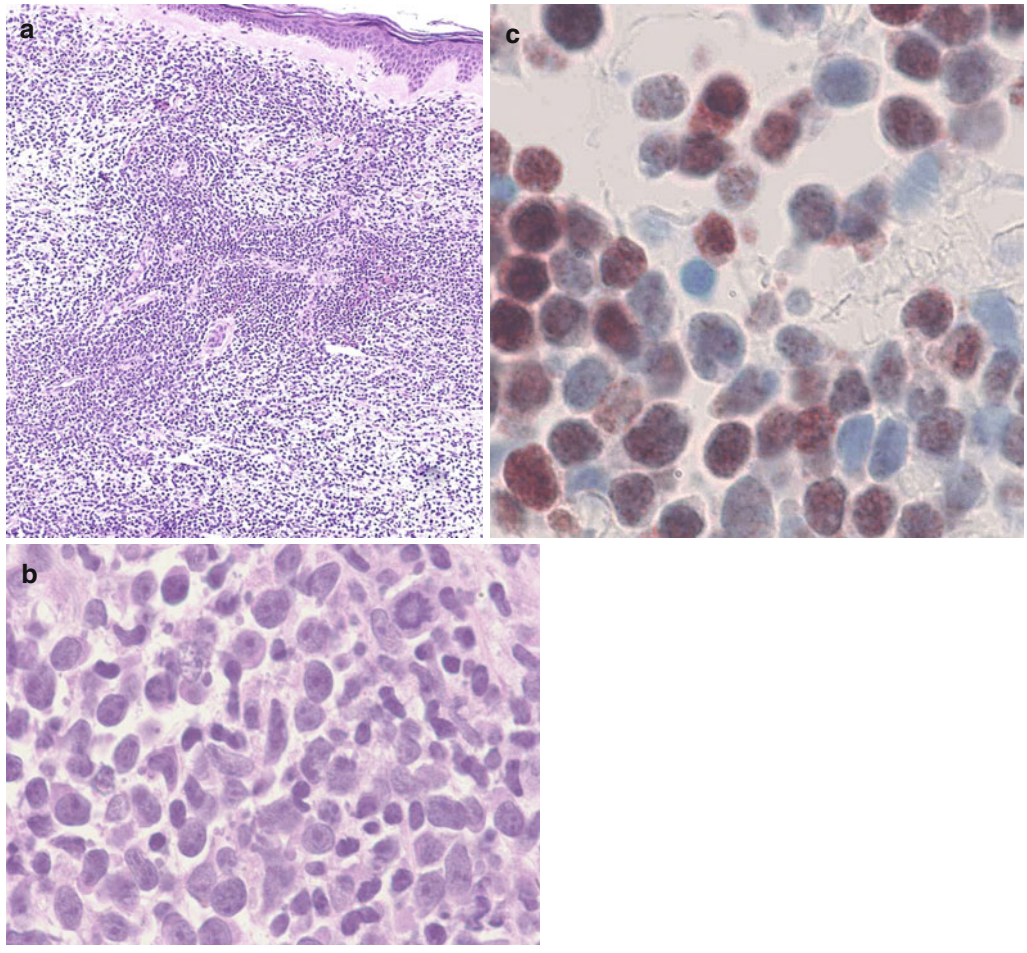

Fig. 16.9 (**a**) Lymphoblastic lymphoma in skin. (**b**) Lymphoblasts with abnormal mitosis, finely dispersed chromatin. (**c**) TdT nuclear-positive lymphoblasts

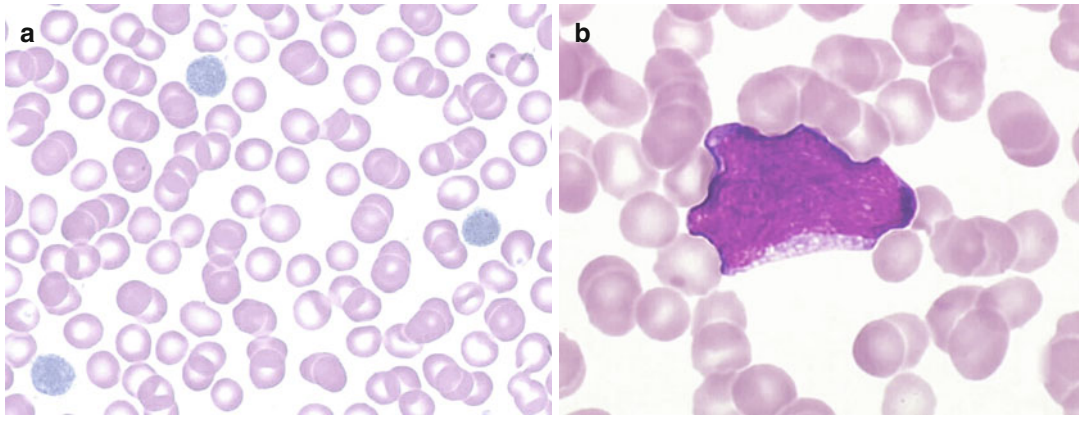

Fig. 16.10 (**a**) Circulating cerebriform lymphocytes and (**b**) circulating blast, in oil magnification, to contrast the nuclear chromatin pattern and contours

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