Lymphohistiocytic and Granulomatous Dermatitis

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May P. Chan

Kikuchi-Fujimoto Lymphohistiocytic Skin Lesion

Introduction

Kikuchi-Fujimoto disease (KFD) is a self-limited histiocytic necrotizing lymphadenitis of unknown etiology. Many potential causative agents have been proposed, including Epstein-Barr virus (EBV) (Yen et al. 1997), human herpesvirus-6 (HHV-6) (Sumiyoshi et al. 1993), and parvovirus B19 (Zhang et al. 2007), but subsequent confirmatory studies failed to validate direct causality (Hollingsworth et al. 1994; George et al. 2003; Kim et al. 2010).

Diagnosis of KFD requires histologic demonstration of nodal or extranodal tissue necrosis showing abundant histiocytes with karyorrhectic debris but distinctly lacking neutrophilic response (Fujimoto et al. 1972; Kikuchi 1972). Up to 40 % of patients with KFD develop skin eruption, which is the focus of this discussion.

Clinical Features

Kikuchi-Fujimoto disease most often affects young Asians under 40 years of age, with a slight female predilection (Kim et al. 2010). The clinical hallmarks of KFD are fever and cervical lymphadenopathy, although infrequently other lymph nodes may also be involved (Fujimoto et al. 1972; Kikuchi 1972). The skin is the most common extranodal site of involvement. Clinically, the cutaneous eruptions are relatively nonspecific but most commonly described as "rash," erythematous macules, patches, papules, or plaques (Atwater et al. 2008). The upper body including the face is typically affected (Spies et al. 1999; Kim et al. 2010). The skin lesions may precede, follow, or develop simultaneously with the lymphadenopathy (Kim et al. 2010).

Kikuchi-Fujimoto disease usually affects otherwise healthy individuals. Association with other diseases is relatively rare and, if found, largely those of autoimmune disorders (Sopeña et al. 2012). Aside from systemic lupus erythematosus, which is a close mimic and may be a related disorder of KFD, other autoimmune conditions such as antiphospholipid syndrome, autoimmune thyroiditis, Sjögren's syndrome, and autoimmune hepatitis have also been reported in patients with KFD (Papaioannou et al. 2002; Santana et al. 2005; Paradela et al. 2008; Shusang et al. 2008; Cheng et al. 2010; Vassilakopoulos et al. 2010; Go et al. 2012).

Histopathology

The most common finding in the skin lesions of KFD is a lymphohistiocytic infiltrate associated

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H.D. Cualing et al. (eds.), *Cutaneous Hematopathology*,
DOI 10.1007/978-1-4939-0950-6_13,

with non-neutrophilic karyorrhectic debris. The infiltrate involves the superficial and deep dermis and may extend into the subcutis (Atwater et al. 2008; Kim et al. 2010), often with accentuation around blood vessels and adnexal structures (Aqel et al. 1997) (Fig. 13.1). In addition to the predominance of phagocytic histiocytes, the infiltrate is also composed of crescentic macrophages and plasmacytoid monocytes similar to those described in nodal KFD (Spies et al. 1999). Crescentic macrophages are characterized by pale cytoplasm and eccentric U-shaped to crenelated nuclei pushed against the cell membrane (Fig. 13.2 and periphery of Fig. 13.3), whereas plasmacytoid monocytes are usually smaller and ovoid, with purplish cytoplasm and round basophilic nuclei (Fig. 13.3 and periphery of Fig. 13.2). The lymphocytes range from small to medium in size and may appear slightly atypical. The karyorrhectic debris is composed of nuclear dusts in the absence of neutrophils (Fig. 13.4). Another common finding is vacuolar interface change with necrotic keratinocytes (Fig. 13.5). Other histologic changes reported in over 10 % of cases include parakeratosis, papillary dermal edema, mucin deposition, and panniculitis. Plasma cells and eosinophils have been observed only in a small number of cases. The diagnostic criteria for cutaneous KFD as proposed by Kim et al. are listed in Table 13.1 (Kim et al. 2010).

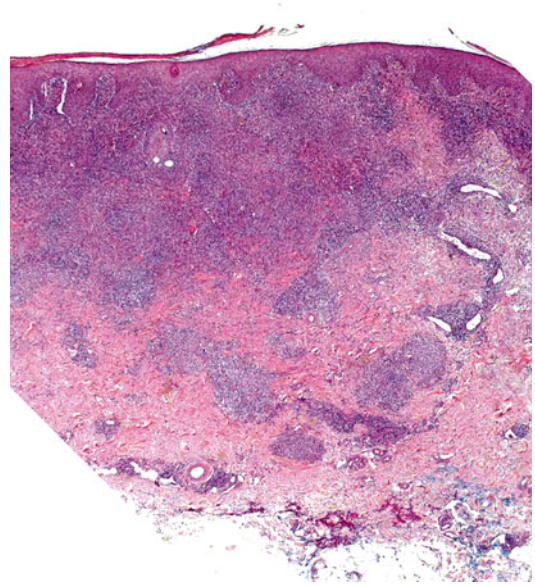

Fig. 13.1 Cutaneous lesion of Kikuchi-Fujimoto disease (KFD). Low magnification shows a brisk lymphoid infiltrate involving the superficial to deep dermis, with accentuation around blood vessels and adnexal structures (Courtesy of Dr. Hernani Cualing)

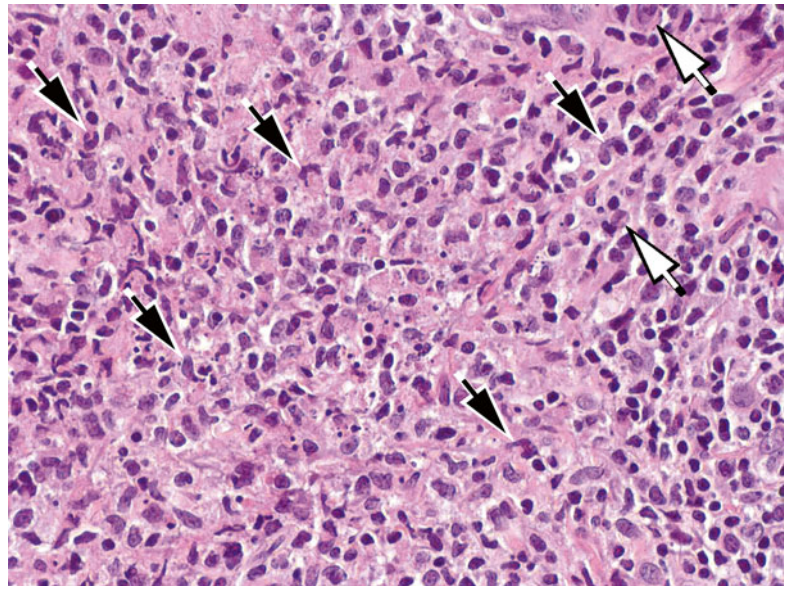

Fig. 13.2 Cutaneous lesion of KFD. The infiltrate in KFD consists of many crescentic macrophages containing pale cytoplasm and eccentric nuclei compressed into a U-shaped crescent against the cell membrane (*black arrows*). There are scattered karyorrhectic debris, but neutrophils are notably absent. Few plasmacytoid monocytes are also present at the periphery of this photomicrograph (*white arrows*) (Courtesy of Dr. Hernani Cualing)

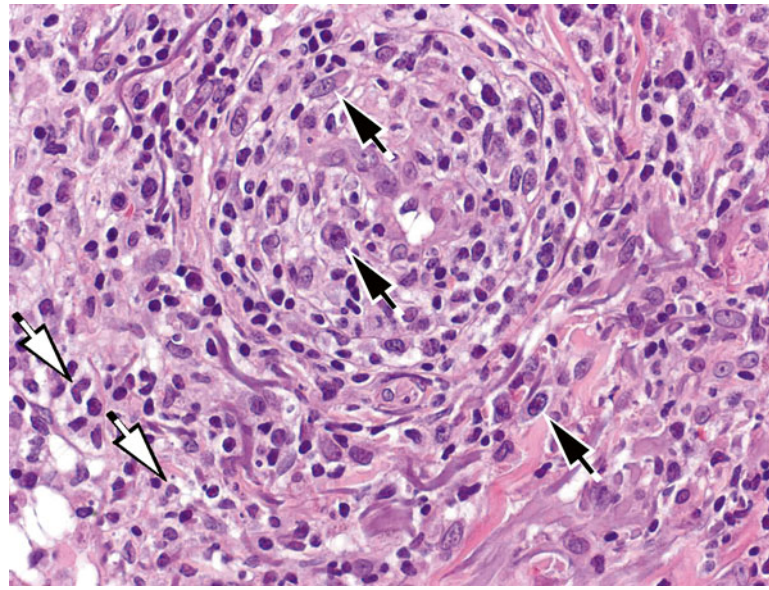

Fig. 13.3 Cutaneous lesion of KFD. Several plasmacytoid monocytes are present in the perivascular infiltrate. Plasmacytoid monocytes contain scant cytoplasm and relatively small, round, and dark nuclei resembling plasma cells (*black arrows*). Few crescentic macrophages are also present at the periphery of this photomicrograph (*white arrows*) (Courtesy of Dr. Hernani Cualing)

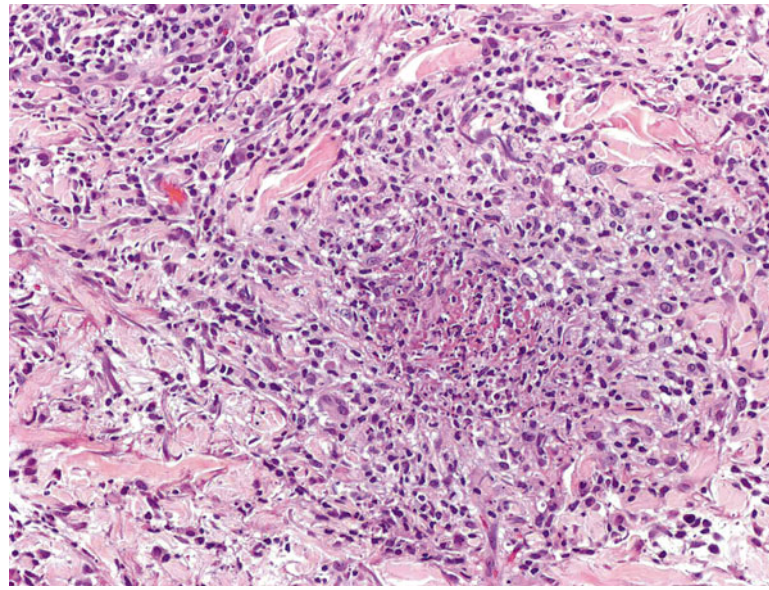

Fig. 13.4 Cutaneous lesion of KFD. A small necrotic focus is present amidst the lymphohistiocytic infiltrate. There is prominent karyorrhexis in the absence of neutrophils (Courtesy of Dr. Hernani Cualing)

Immunophenotype

The lymphocytes in the skin lesions of KFD are CD3-positive T cells. In most cases, there are slightly more CD8-positive cytotoxic T cells than CD4-positive helper T cells (Kim et al. 2010). Only rare cells express CD30 and TIA-1 (Spies et al. 1999). The histiocytes are positive for CD68 (Fig. 13.6), CD163, and myeloperoxidase (MPO) (Pileri et al. 2001; Fernandez-Flores et al. 2008). In particular, the plasmacytoid monocytes also express CD123 but are negative for fascin, suggesting an immature dendritic cell phenotype (Pilichowska et al. 2009). Occasional cases may demonstrate EBV, HHV-6, parvovirus B19, and other viral

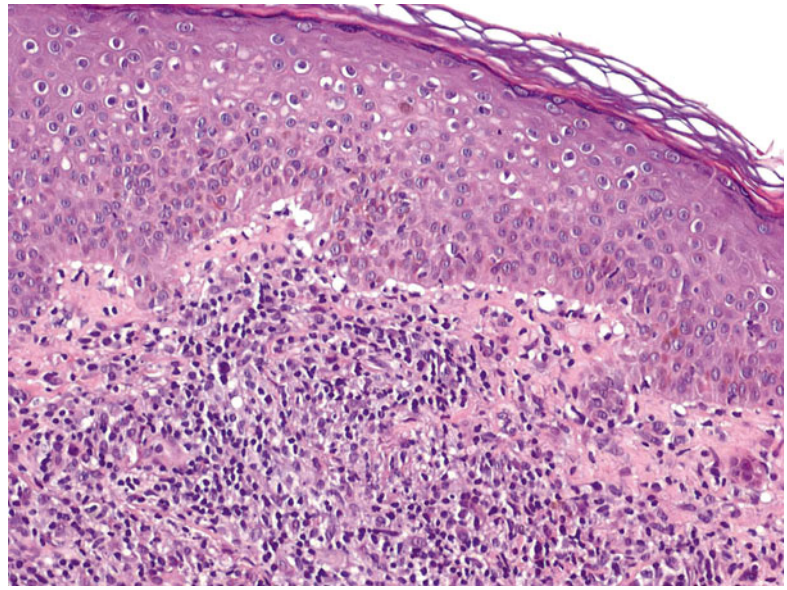

Fig. 13.5 Cutaneous lesion of KFD. The epidermis demonstrates basal vacuolar degeneration consistent with vacuolar interface dermatitis (Courtesy of Dr. Hernani Cualing)

Table 13.1 Diagnostic criteria for the cutaneous lesions of Kikuchi-Fujimoto disease

Major criteria	Minor criteria
1. Presence of karyorrhexis	1. Presence of interface dermatitis
2. Absence of neutrophils	2. Presence of inflammatory cell infiltrate in the reticular dermis or subcutaneous fat
	3. The histiocytes are predominant cells of the inflammatory cells
	4. The CD8-positive cytotoxic T lymphocytes are predominant lymphocytes

Diagnosis requires fulfillment of two major criteria and at least two minor criteria
Reprinted from Kim et al. (2010). With permission from Elsevier

antigens in the atypical lymphocytes by immunohistochemistry, in situ hybridization, or polymerase chain reaction studies (Sumiyoshi et al. 1993; Yen et al. 1997; Zhang et al. 2007).

Genetics and Molecular Findings

A T-cell receptor gene rearrangement study has shown the vast majority of KFD cases to be polyclonal. Although some cases demonstrated oligoclonality at the beta and/or gamma loci, spontaneous resolution of all cases within 6 months supports a benign immune reaction (Lin et al. 2002). A Japanese study examined the HLA class II genes (HLA-DR, HLA-DQ, and HLA-DP) and found significantly higher allele frequencies of DPA1*01 and DPB1*0202 in patients with KFD compared to normal controls (Tanaka et al. 1999). These findings may explain the higher incidence of KFD in Asians as the DPB1*0202 allele is extremely rare in Caucasians and Negroids but relatively frequent in Asians (Imanishi et al. 1992). Another study reported familial occurrence of KFD in two non-twin sisters with identical HLA phenotypes, further suggesting genetic predisposition to the disease (Amir et al. 2002).

Prognosis or Course

Most cases of KFD resolve without intervention within 2–6 months (Spies et al. 1999; Lin et al. 2002). Recurrence is observed in about 15–20 % of patients and is associated with a higher incidence of autoimmune diseases and positive antinuclear antibodies (ANA) (Song et al. 2009; Cheng et al. 2010). While skin involvement alone

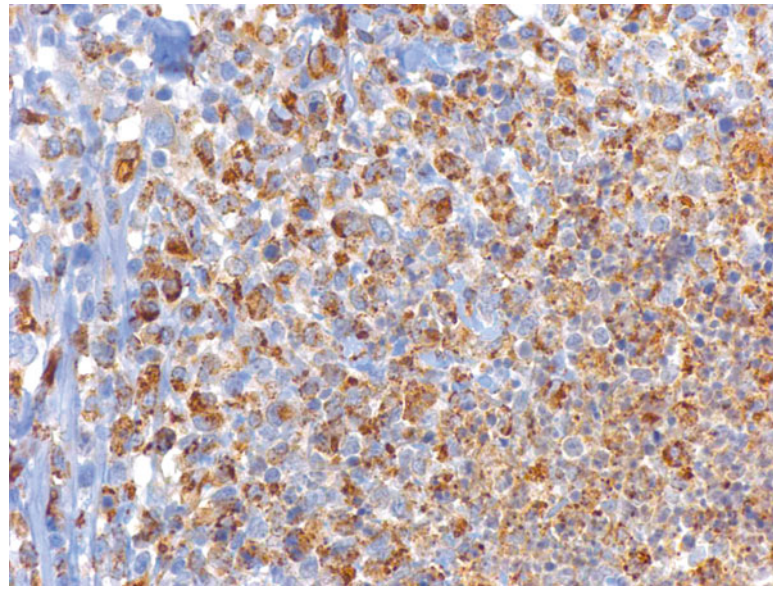

Fig. 13.6 Cutaneous lesion of KFD. CD68 highlights many histiocytes in the infiltrate (Courtesy of Dr. Hernani Cualing)

does not seem to be associated with recurrence or development of autoimmune diseases, interface dermatitis was found to be a consistent finding in cases that evolved into systemic lupus erythematosus (Paradela et al. 2008). Long-term follow-up of patients with skin involvement and/or positive ANA is therefore recommended (Cheng et al. 2010).

Differential Diagnosis

The distinction between the skin lesions of KFD and cutaneous lupus erythematosus (LE) can be extremely challenging due to significant histologic overlap, namely, interface dermatitis, dermal mucin deposition, perivascular lymphocytic infiltrate, and panniculitis. The presence of prominent non-neutrophilic karyorrhexis, however, is not a feature of LE. Plasma cells are often present in LE but usually absent or sparse in KFD. Direct immunofluorescence study is useful in confirming LE and excluding KFD when a characteristic "lupus band" (granular immune deposits) is present at the dermoepidermal junction (Kim et al. 2010).

The infiltrate in the cutaneous lesions of KFD may be brisk and, in conjunction with the presence of atypical lymphocytes and larger monocytes, may raise concern for lymphoma. In particular, cases demonstrating subcutaneous involvement by histiocytes, CD8-positive lymphocytes, and karyorrhectic debris may bear close resemblance to subcutaneous panniculitis-like T-cell lymphoma (SPLTCL). However, the absence of rimming of adipocytes by atypical lymphocytes and the significant dermal (and sometimes epidermal) involvement in KFD would help in its distinction from SPLTCL. An immunoprofile showing CD8 predominance and minimal CD56 and TIA-1 staining also helps to exclude other types of T-cell lymphomas. Molecular analysis for T-cell receptor gene rearrangement may be employed to rule out a clonal process in challenging cases.

A comparison of the histologic findings in KFD, LE, and SPLTCL is summarized in Table 13.2.

Rosai-Dorfman Skin Lesion

Introduction

Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a rare histiocytosis of unclear etiology. An infectious cause has long been suspected but

Table 13.2 Comparison of the skin lesions of Kikuchi-Fujimoto disease (KFD), lupus erythematosus (LE), and subcutaneous panniculitis-like T-cell lymphoma (SPLTCL)

Histologic features	KFD	LE	SPLTCL
Interface dermatitis with necrotic keratinocytes	+	+	–
Dermal infiltrate	+ (may be brisk)	+ (mild)	–
Subcutaneous infiltrate	+/–	+ in lupus panniculitis	+
Rimming of adipocytes by atypical lymphocytes	–	–	+
CD8-predominant T cells	+	+	+
Crescentic macrophages	+	–	+/–
Plasmacytoid monocytes	+	+	–
Non-neutrophilic karyorrhexis	+	–/rare	+
Mucin	+/–	+	–
T-cell receptor gene rearrangement	Polyclonal	Polyclonal	Monoclonal

+, present; –, absent

has not been confirmed. While the condition primarily affects the lymph nodes, up to 43 % of cases also demonstrate extranodal involvement. Skin involvement is present in 10 % of cases and is the most common extranodal manifestation (Rosai and Dorfman 1972). Over the past decades, a rare, pure cutaneous form of RDD (C-RDD) has been increasingly reported and recognized as a distinct clinical entity. Regardless of site, RDD is characterized by the presence of Rosai-Dorfman cells ("RD cells") which engulf intact inflammatory cells in a process known as emperipolesis. This discussion focuses on the skin lesions of RDD.

Clinical Features

Systemic RDD has the highest incidence among African and Caucasian young adults. The disease classically manifests as bilateral, massive, but painless cervical lymphadenopathy, accompanied by fever, leukocytosis, and polyclonal hypergammaglobulinemia (Rosai and Dorfman 1969, 1972). Skin lesions in systemic RDD are usually multiple (Thawerani et al. 1978). In contrast, pure C-RDD mainly affects Asians with a median age of over 40 years (Brenn et al. 2002; Lu et al. 2004; Wang et al. 2006; Kong et al. 2007). Three types of skin lesions have been described, including papulonodular, indurated plaque, and tumor types (Kong et al. 2007). The most common papulonodular type refers to clusters of papules and/or nodules measuring up to 1.5 cm in diameter. The lesions may be erythematous, violaceous, or brown in color. The indurated plaque type refers to flat-topped hyperpigmented plaques with a palpable infiltrated border. Scattered papules may also be found within or surrounding the plaques. The tumor type is the rarest form which presents as exophytic large masses with or without central ulceration.

A case registry study has shown that approximately 10 % of patients with systemic RDD exhibit signs of immune dysfunction (Foucar et al. 1984). Interestingly, a link between systemic RDD and autoimmune lymphoproliferative syndrome (ALPS) has been proposed due to the overlapping clinical features (lymphadenopathy and hypergammaglobulinemia) and the finding of nodal RD cells in over 40 % of patients with ALPS type Ia (Maric et al. 2005). These associations, however, have not been demonstrated in pure C-RDD. Other individual case reports have described the occurrence of RDD in patients with lymphoma, carcinoma, melanoma, sickle cell disease, and morphea; however, no clear association has been established (Ratzinger et al. 2003; Stebbing et al. 2007; Moore et al. 2008; Chappell et al. 2009).

Histopathology

The cutaneous lesions of RDD are composed of a nodular or diffuse infiltrate which may be purely dermal, dermal and subcutaneous, or purely

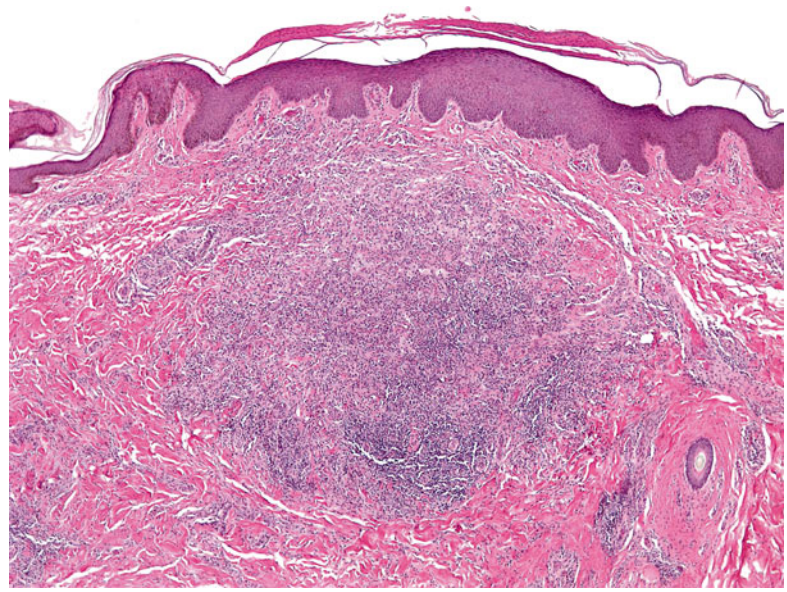

Fig. 13.7 Cutaneous lesion of Rosai-Dorfman disease (RDD). A dense lymphoid infiltrate is present in the dermis

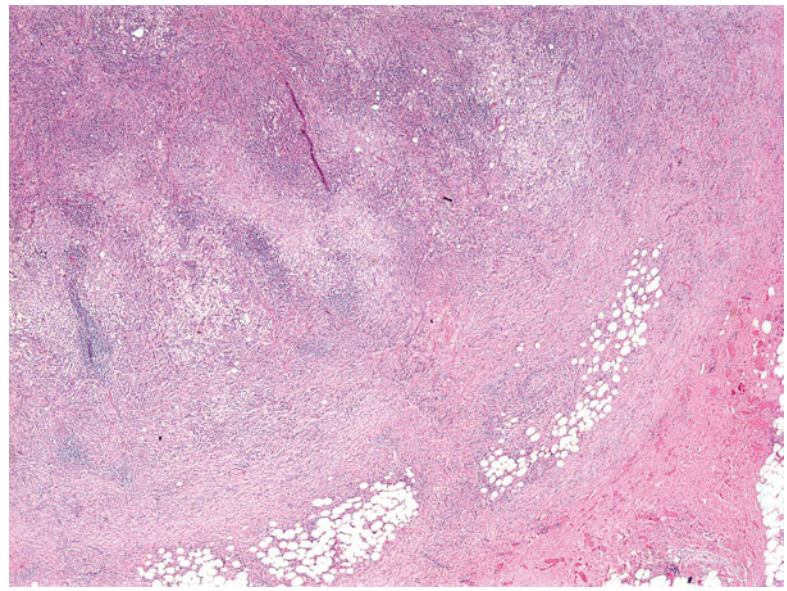

Fig. 13.8 Cutaneous lesion of RDD. This example shows extensive involvement of the subcutaneous fat

subcutaneous (Figs. 13.7 and 13.8). The overlying epidermis is uninvolved but may be attenuated. Amidst the infiltrate are a variable number of RD cells, which are large polygonal histiocytes containing intact lymphocytes, plasma cells, and/or neutrophils within their pale cytoplasm (Figs. 13.9, 13.10, and 13.11). This process is referred to as "emperipolesis" and is the diagnostic hallmark of this disease. RD cells may sometimes be found within dilated lymphatics (Chu and LeBoit 1992). The rest of the infiltrate consists of lymphocytes, plasma cells, non-RD histiocytes, and neutrophils. Germinal centers and microabscesses may be present (Lu et al. 2004; Kong et al. 2007). A xanthomatous component has been described in a subset of cases (Thawerani et al. 1978; Quaglino et al. 1998), as well as coexisting foci of Langerhans cell histiocytosis

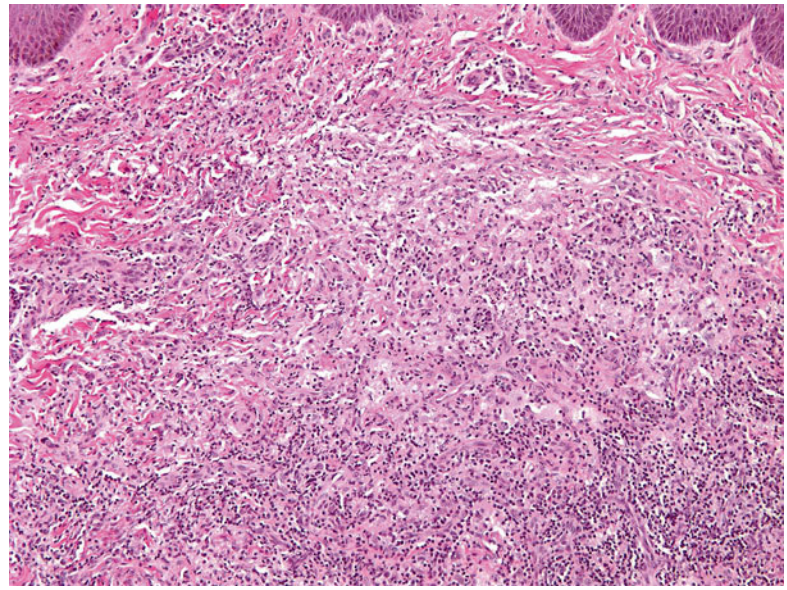

Fig. 13.9 Cutaneous lesion of RDD. Scattered large pale histiocytes are admixed with a dense lymphocytic infiltrate

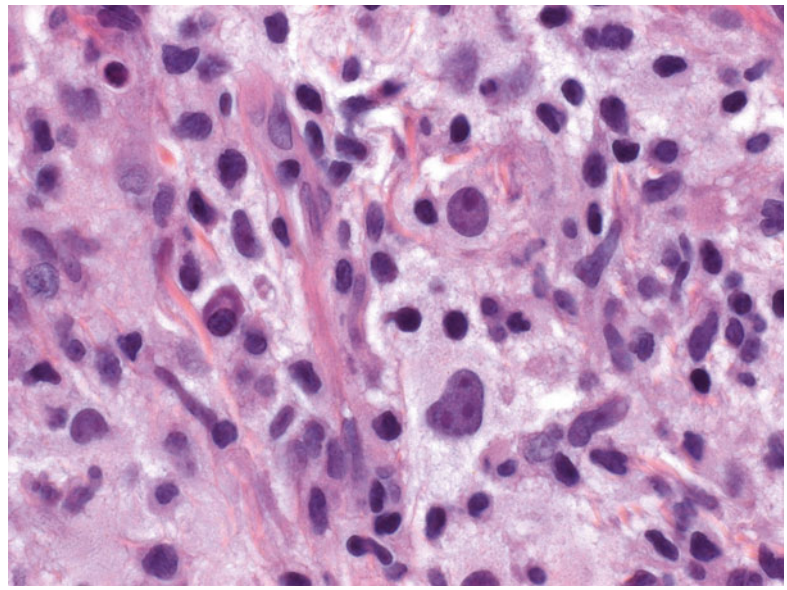

Fig. 13.10 Emperipolesis in cutaneous RDD. Intact lymphocytes are present within the abundant pale cytoplasm of several large Rosai-Dorfman (RD) cells (Courtesy of Dr. David P. Arps, Department of Pathology, University of Michigan)

(LCH) (Wang et al. 2002, 2006; Kong et al. 2007). Eosinophils are rare except in the foci of LCH (Cangelosi et al. 2011). Many cases show various degrees of stromal fibrosis with or without a storiform pattern (Kong et al. 2007; Kuo et al. 2009). When the subcutis is involved, a panniculitis-like pattern with secondary vasculitis may be observed (Kong et al. 2007).

No reliable histologic feature is helpful in distinguishing C-RDD from the cutaneous lesions of systemic RDD. A small series has found pseudoepitheliomatous hyperplasia and eosinophils to be present only in one case of C-RDD but not in systemic RDD; however, the small number of cases precludes any definitive conclusion (Chu and LeBoit 1992). Human herpesvirus-6 has

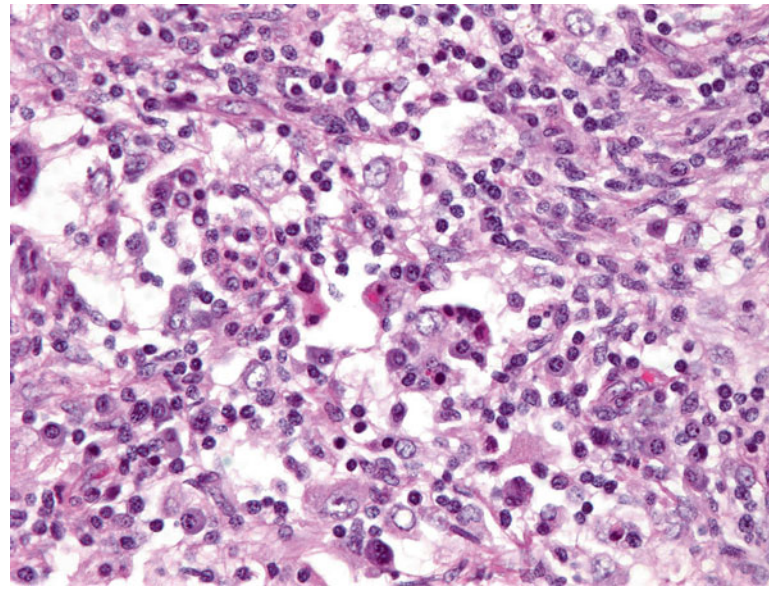

Fig. 13.11 Emperipolesis in cutaneous RDD. Frequent plasma cells are present, some of which are present within the cytoplasm of RD cells along with lymphocytes and few neutrophils

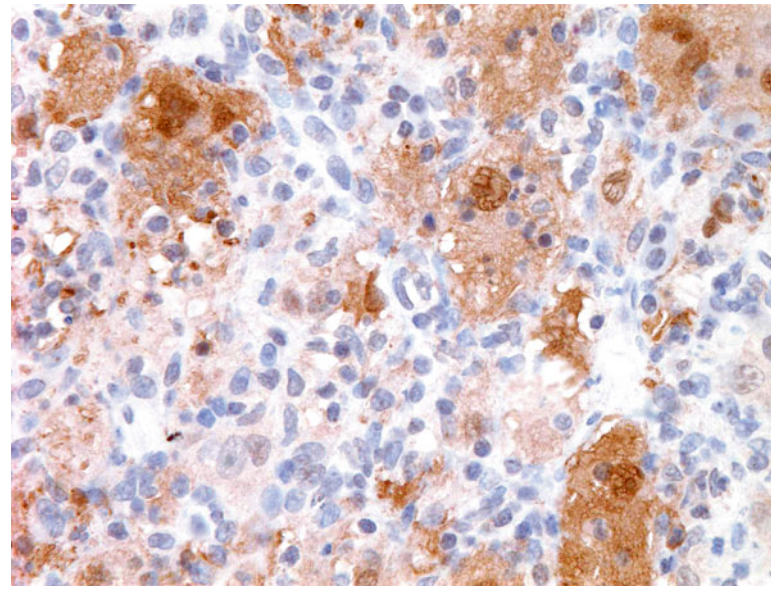

Fig. 13.12 Emperipolesis in cutaneous RDD. S100 immunostain highlights the nuclei and the cytoplasm of RD cells, while the engulfed lymphocytes are negative

been detected in some cases of systemic RDD (Levine et al. 1992; Luppi et al. 1998) but not in C-RDD (Ortonne et al. 2002). Other rarely detected viruses include parvovirus B19, EBV, and polyomavirus (Levine et al. 1992; Mehraein et al. 2006; Al-Daraji et al. 2010). However, the causal role of these agents has not been confirmed due to the limited number of cases.

Immunophenotype

The RD cells are positive for S100 (Bonetti et al. 1987) (Fig. 13.12), CD68, and lysozyme (Kong et al. 2007). Immunoreactivity for fascin and factor XIIIa has also been reported (Perrin et al. 1993; Jaffe et al. 1998). Unlike Langerhans cells, RD cells lack Birbeck granules and are negative

Table 13.3 Comparison of cutaneous Rosai-Dorfman disease (RDD) with Langerhans cell histiocytosis (LCH) and xanthogranuloma (XG)

	RDD	LCH	XG
Characteristic histiocytes	"RD cells" with abundant pale cytoplasm showing emperipolesis of lymphocytes, plasma cells, and/or neutrophils	Langerhans cells with moderate amount of eosinophilic cytoplasm and reniform/folded nuclei	Xanthomatous cells with foamy cytoplasm
Other common inflammatory cells	Lymphocytes, plasma cells	Eosinophils	Variable
Immunophenotype	RD cells (+) S100, CD68, lysozyme (−) CD1a, langerin	Langerhans cells (+) S100, CD1a, langerin (−) CD68, lysozyme	Xanthomatous cells (+) CD68, lysozyme (+/−) S100 (−) CD1a, langerin

for CD1a and langerin (Rosai and Dorfman 1972; O'Malley et al. 2010). The lymphocytes in RDD are a mixture of T and B cells with T-cell predominance (Yu et al. 2007). The plasma cells are polytypic (Motta et al. 2005). Interestingly, the vast majority of plasma cells in both nodal and extranodal RDD are positive for IgG. There is also an increased proportion of IgG4 positive cells, with a mean IgG4/IgG ratio of over 30 % (Kuo et al. 2009; Zhang et al. 2013). Taken together with the frequent finding of stromal fibrosis, a possible relationship between RDD and IgG4-related sclerosing disease has been suggested and deserves further investigation.

Genetics and Molecular Findings

Polyclonality has been demonstrated in two cases of RDD (Paulli et al. 1995). Despite the possible relationship between ALPS and RDD, no mutation in the Fas-encoding gene has been illustrated in the few RDD cases studied (Maric et al. 2005).

Prognosis or Course

RDD typically runs a benign and indolent course. Spontaneous remission of C-RDD occurs in a subset of patients, while the remainder of cases may be treated effectively by surgical excision (Lu et al. 2004; Kong et al. 2007). Other treatment modalities include high-dose thalidomide and radiation therapy for extensive or persistent diseases in the skin or soft tissue (Lu et al. 2004; Al-Daraji et al. 2010).

Differential Diagnosis

RDD needs to be distinguished from other histiocytoses as the clinical manifestations and prognosis may differ significantly. In Langerhans cell histiocytosis, there are clusters or sheets of Langerhans cells with pale eosinophilic cytoplasm and reniform nuclei, often admixed with a large number of eosinophils. Both Langerhans cells and RD cells are positive for S100, whereas CD1a and langerin are expressed by Langerhans cells only. As mentioned above, foci of LCH may be present and do not exclude a diagnosis of C-RDD. Similarly, xanthogranuloma may enter the differential diagnosis when a conspicuous population of xanthomatous cells is present. Recognition of emperipolesis by RD cells, which may be aided by the use of S100 immunostain, should allow for the correct diagnosis of RDD. A comparison of RDD with other cutaneous histiocytoses is summarized in Table 13.3.

Histologic overlap between soft tissue RDD and inflammatory pseudotumor is known to be a diagnostic pitfall. Emperipolesis may be inconspicuous in the soft tissue as the RD cells tend to be more spindle and may be overshadowed by a dense inflammatory infiltrate, including numerous plasma cells which are also characteristic of

inflammatory pseudotumor (Veinot et al. 1998; Kroumpouzos and Demierre 2002). Some authors have proposed a temporal sequence in which histiocyte-rich RDD may transform to fibroblast-rich inflammatory pseudotumor (Govender and Chetty 1997), a hypothesis that has not been proven. An S100 immunostain to highlight any RD cells is probably prudent before rendering a diagnosis of inflammatory pseudotumor in the soft tissue. Lastly, as with other plasma cell-rich conditions, illustration of polytypic light-chain expression by either immunohistochemistry or in situ hybridization would help to exclude a plasma cell or B-cell neoplasm.

Sarcoidosis

Introduction

Sarcoidosis is a multisystem granulomatous disorder. Its incidence is highest among African Americans and peaks in the third to fourth decades of life (Rybicki et al. 1997; Hosoda et al. 2002). The pathogenesis remains elusive, but current data point to immune dysregulation following exposure to certain antigens in genetically predisposed individuals. Due to the diverse clinical morphologies of cutaneous sarcoidosis, skin biopsy is important in excluding other dermatologic conditions. A confirmed diagnosis should prompt clinical evaluation for systemic involvement.

Clinical Features

Sarcoidosis mainly affects the lungs, lymph nodes, and skin, although virtually any organs may be affected. Cutaneous involvement is present in about 25 % of patients with sarcoidosis (Newman et al. 1997) and is the first presenting sign of systemic disease in a third of these patients (Costabel et al. 2007). Isolated cutaneous sarcoidosis without evidence of systemic involvement is less common. The skin lesions may present as maculopapules, infiltrated plaques, subcutaneous nodules, lupus pernio, or infiltrated scars (Mañá et al. 1997; Haimovic et al. 2012). Papular lesions typically occur on the face, while plaques are most commonly found on the buttocks, back, and other extensor surfaces (Elgart 1986). Lupus pernio refers to violaceous induration on the nose and cheeks which may result in significant disfiguration (James 1992). Verrucous sarcoidosis is an uncommon variant which may mimic squamous cell carcinoma clinically (Stockman et al. 2013). Another rare variant is syringotropic sarcoidosis, which presents as multiple erythematous patches or plaques on the lower extremities (Hayakawa et al. 2013). Interestingly, the sweating responses to thermal stress were reported to be markedly diminished in these cases. Other uncommon presentations include annular, photodistributed, ichthyosiform, atrophic, ulcerative, and hypopigmented forms (Haimovic et al. 2012).

Associations between sarcoidosis and various malignancies have been well documented. These include lymphoma, leukemia, cutaneous squamous cell carcinoma, lung cancer, and many others (Brincker and Wilbek 1974; Ji et al. 2009). Sarcoidosis precedes the diagnosis of malignancy by an average of 8 years (Alexandrescu et al. 2011). The risk is highest during the first year following hospitalization for sarcoidosis (Ji et al. 2009). The term "sarcoidosis-lymphoma syndrome" was used to describe the development of lymphoma within 2 years following the diagnosis of sarcoidosis (Brincker 1986). Other reported associations include primary biliary cirrhosis, interferon therapy, and hepatitis C (Kishor et al. 2008; Lee et al. 2011; North and Mully 2011).

Histopathology

Regardless of site, sarcoidosis is characterized by well-formed, non-necrotizing granulomas. The granulomas are usually numerous and extensively infiltrate the affected organ (Fig. 13.13). The discrete and rounded granulomas typically lack a significant lymphocytic infiltrate, hence the description of "naked granulomas" (Fig. 13.14). The granulomas are composed of predominantly epithelioid histiocytes admixed

with scattered multinucleated foreign body-type giant cells (Fig. 13.15). The specificity of "asteroid body" in the giant cells is limited, as it may be encountered in sarcoidosis as well as other granulomatous conditions. The granulomas sometimes display a periadnexal and/or perivascular distribution (Mangas et al. 2006). Scar sarcoidosis refers to sarcoidosis involving a preexisting scar, including post-herpes zoster scars (Selim et al. 2006). An interesting finding in the syringotropic variant was the profoundly decreased expression of dermcidin and aquaporin 5 in the affected sweat glands (Hayakawa et al. 2013). In verrucous sarcoidosis, there is verrucous pseudoepitheliomatous hyperplasia of the overlying epidermis (Stockman et al. 2013). A study has expanded the histologic spectrum of cutaneous sarcoidosis, including tuberculoid granulomas, interstitial granulomas, focal necrosis, and lichenoid inflammation (Ball et al. 2004). The exclusion of infection, however, is of paramount importance in light of these atypical presentations, despite an established diagnosis of systemic sarcoidosis in these patients.

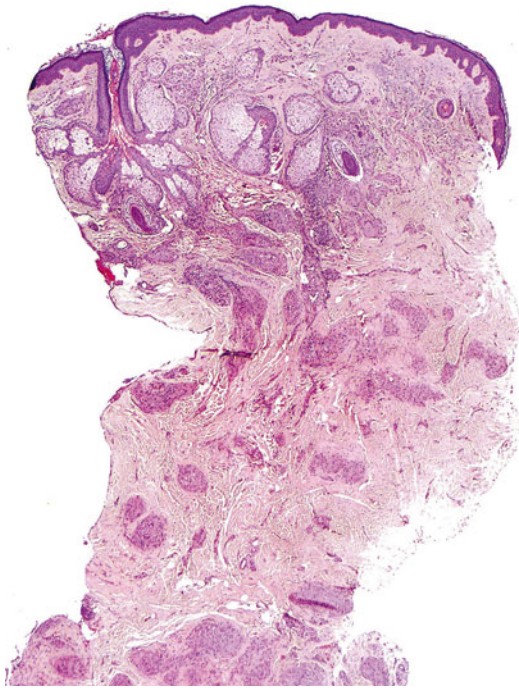

Fig. 13.13 Cutaneous sarcoidosis. Numerous discrete, rounded granulomas are present throughout the dermis

Although once regarded as an excluding factor, polarizable foreign bodies are now recognized as a fairly common finding in sarcoidosis. Approximately 25 % of the cutaneous lesions of sarcoidosis may contain polarizable foreign bodies (Kim et al. 2000; Mangas et al. 2006). The foreign bodies are composed of calcium, phosphorus, silicon, and aluminum and are thought

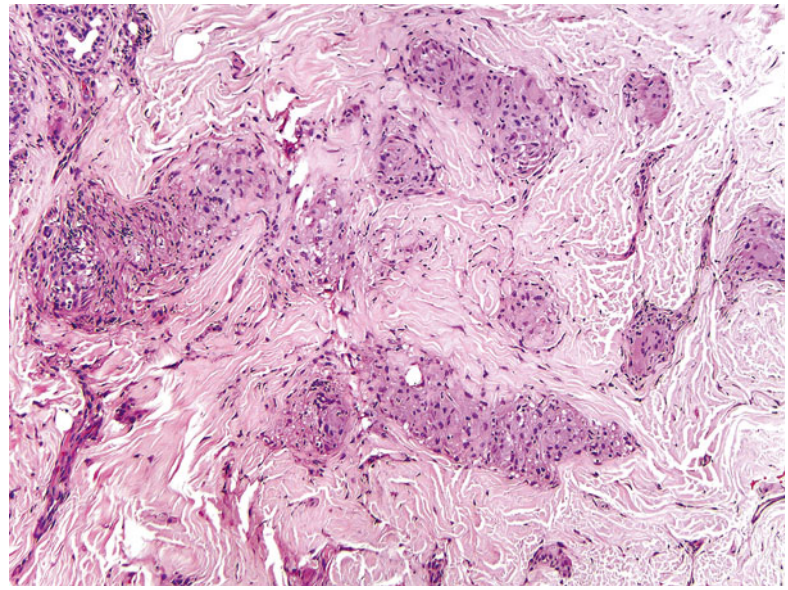

Fig. 13.14 Cutaneous sarcoidosis. The so-called naked granulomas are free of surrounding lymphocytic infiltrate

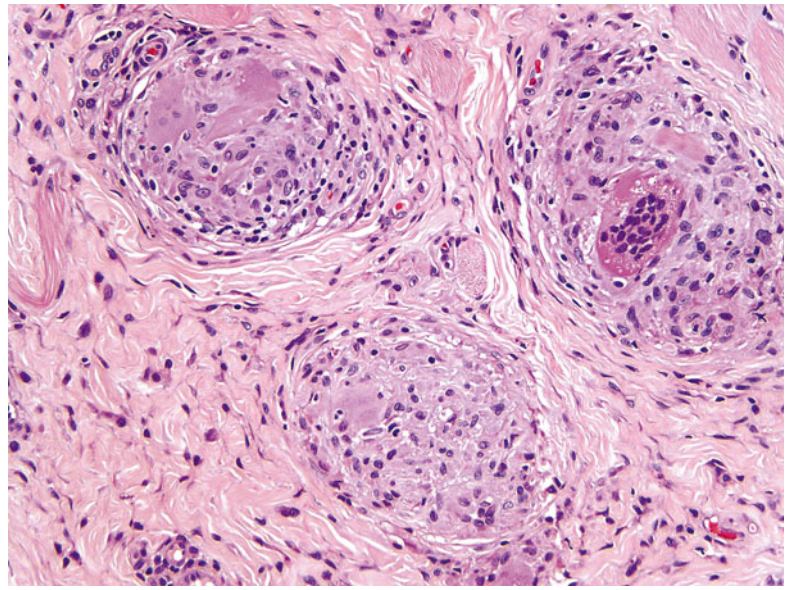

Fig. 13.15 Cutaneous sarcoidosis. Discrete sarcoidal granulomas are composed of epithelioid histiocytes and occasional foreign body-type giant cells

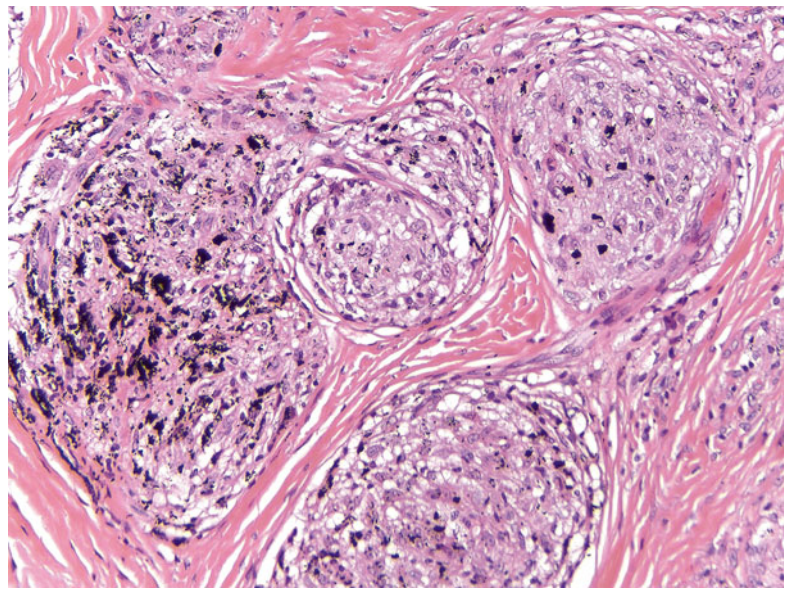

Fig. 13.16 Sarcoidal granulomatous reaction to tattoo pigment

to serve as a nidus for granuloma formation secondary to an overactive cellular immune response in sarcoidosis patients (Walsh et al. 1993). Some cases of sarcoidal granulomatous response to tattoo granules (Fig. 13.16) or silicone implants may be followed by subsequent development of more widespread sarcoidosis, further supporting a systemic rather than localized disease in these patients (Hanada et al. 1985; Teuber et al. 1994).

Immunophenotype

The histiocytes in the sarcoidal granulomas are immunoreactive for CD68 and CD163. The lymphocytes present in sarcoidosis are predominantly CD3-positive and CD4-positive T-helper cells (de Jager et al. 2008). These findings are in keeping with the current understanding of the crucial role of T-cell activation in granuloma formation (Agostini et al. 2000; Chen and Moller 2008).

Genetics and Molecular Findings

The initial step in the formation of a sarcoidal granuloma involves recognition and phagocytosis of a putative antigen by the antigen-presenting cell (APC) (Co et al. 2004). The APC in turn presents any nondegradable particles to a T cell, a process that triggers a cellular immune response with the secretion of multiple cytokines including tumor necrosis factor (TNF-α), interleukins (IL-12, IL-15, and IL-18), and macrophage inflammatory protein (MIP-1), which drive the formation of granulomas (Agostini et al. 2000). The T cells in sarcoidosis are polyclonal (Pfaltz et al. 2011).

Familial clustering of sarcoidosis has been well documented (Iannuzzi 1998). Having a first-degree relative with sarcoidosis corresponds to a fivefold increase in one's risk of developing the disease (Rybicki et al. 2001). The most widely studied genes are those in the major histocompatibility complex on chromosome 6 which encode the human leukocyte antigens (HLAs). Various studies have correlated different HLA phenotypes with specific manifestations and severity of sarcoidosis. For example, HLA-B13 and HLA-B35 are associated with early disease onset, whereas HLA-A30, HLA-B8, HLA-DR3, and HLA-DR4 are associated with late disease onset (Smith et al. 2008). Studies on cytokine genes such as tumor necrosis factor (TNF) and interferon (IFN) and receptor genes such as Toll-like receptor (TRL4) and butyrophilin-like protein (BTNL2) also reveal possible links to sarcoidosis (Smith et al. 2008). The current data suggest a complex interplay between multiple genes and environmental factors in the pathogenesis of sarcoidosis, which makes genetic studies particularly challenging.

Prognosis or Course

While the majority of cases resolve spontaneously within 2–5 years, up to 10–30 % of cases may persist or progress (Hunninghake et al. 1999; Baughman et al. 2003). The maculopapular lesions have the best clinical outcome, whereas plaque-type lesions and lupus pernio usually run a chronic and progressive course (Veien et al. 1987; James 1992; Samtsov 1992; Mañá et al. 1997). Fibrosis is an unfavorable and irreversible sequela of chronic sarcoidal granuloma.

Differential Diagnosis

Sarcoidosis remains a diagnosis of exclusion. The presence of sarcoidal granulomas in a biopsy should prompt a careful search for microorganisms, in particular fungi and mycobacteria, by Grocott's methenamine silver (GMS) and Ziehl-Neelsen or Fite stains. Although infectious granulomas are more likely to be necrotizing, suppurative, or "tuberculoid" (surrounded by lymphocytes), the absence of these features does not exclude an infectious etiology. Tissue culture is therefore advisable prior to the establishment of a diagnosis of sarcoidosis.

Foreign body granulomas may also mimic sarcoidosis. Examination of the tissue sections under polarized light is often helpful in identifying foreign materials. However, as discussed above, the presence of foreign bodies does not always exclude sarcoidosis. For cases in which the foreign body granulomas display a classic sarcoidal morphology, clinical work-up to rule out sarcoidosis should be considered.

Some cases of cutaneous T-cell lymphoma may consist of a prominent granulomatous component simulating sarcoidosis (Mainguene et al. 1993; Bessis et al. 1996; Telle et al. 1998). A high index of suspicion should be maintained when a lymphocytic infiltrate is present in addition to the epithelioid granulomas. Careful examination for epidermotropism and lymphocytic atypia, followed by immunophenotyping and/or molecular studies, will allow for correct diagnosis of granulomatous mycosis fungoides (Pfaltz et al. 2011). See Chaps. 4 and 6.

Granuloma Annulare

Introduction

Granuloma annulare is a relatively common and self-limited dermatologic condition characterized by palisaded granulomatous dermatitis and

necrobiosis. Many possible pathogenic mechanisms have been proposed; however, none has been universally accepted (Dahl 1985). Cases may be subdivided into localized, generalized, subcutaneous, and perforating forms depending on their clinical and histopathologic presentations. Although most cases of granuloma annulare occur as an isolated phenomenon, its associations with a variety of medical and neoplastic conditions have also been described.

Clinical Features

Granuloma annulare has a predilection for females and young patients under 30 years of age (Dahl 1993; Zax and Callen 1990). In general, the hands and feet are most frequently affected, while the face is often spared; however, involvement of virtually any skin sites has been reported.

The *classic localized form* typically manifests as a limited number of asymptomatic, skin-colored, or pink papules or plaques with an annular or arcuate configuration in the absence of surface changes (Muhlbauer 1980). In the *generalized form*, there are over hundreds of small skin-colored papules widely distributed over the trunk and, to a lesser degree, the extremities (Dabski and Winkelmann 1989). The *subcutaneous form* typically occurs in children (Felner et al. 1997; Grogg and Nascimento 2001), although rarely it may also occur in adults (De Aloe et al. 2006; Salomon et al. 1986). It is characterized by larger and deeper nodules located on the extremities, the buttocks, and/or the scalp (Felner et al. 1997; Politz and Miller 1983). The rare *perforating form* accounts for approximately 5 % of cases and is more likely to affect older patients (Penas et al. 1997). The dorsal hands and other extensor surfaces of the extremities are the most common sites. These lesions often have a pustular or crusted surface owing to the perforating process.

The occurrence of granuloma annulare in patients with coexisting systemic diseases or malignancies has been well documented. Various studies have shown that approximately 10–20 % of patients with granuloma annulare also carry a diagnosis of diabetes (Dabski and Winkelmann 1989; Jelinek 1993; Studer et al. 1996). However, given the relatively high prevalence of diabetes in the general population, this may be a result of coincidence rather than true association (Smith et al. 1997). A different study failed to confirm any statistically significant association between granuloma annulare and type 2 diabetes (Nebesio et al. 2002). Another frequently reported association is human immunodeficiency virus infection (Cohen 1999; Ghadially et al. 1989; Jones and Harman 1989; O'Moore et al. 2000; Toro et al. 1999). Potential links to various neoplastic conditions have also been suggested. These include hematologic malignancies (both lymphomas and leukemias) and, less often, solid tumors (Barksdale et al. 1994; Cohen 2006). Although no definite association has been established, it is suggested that atypical presentation of granuloma annulare—such as those occurring on the face and in older patients—may warrant clinical work-up to exclude an underlying cancer (Li et al. 2003). Other less common associations include Sjögren's syndrome, autoimmune thyroiditis, uveitis, dyslipidemia, hypercalcemia, hepatitis C virus infection, BCG vaccination, and TNF-α treatment (Baker and Pehr 2006; Granel et al. 2000; Kakurai et al. 2001; Oz et al. 2003; Sumikawa et al. 2010; Vazquez-Lopez et al. 2003; Voulgari et al. 2008; Wu et al. 2012).

Histopathology

The histologic hallmark of granuloma annulare is palisading granuloma with central necrobiosis (Fig. 13.17). The histiocytes are typically spindle in appearance, although occasional multinucleated giant cells may also be seen (Fig. 13.18). The central necrobiotic zone is composed of degenerated collagen which tends to appear more eosinophilic, swollen, and/or fragmented compared to the normal dermal collagen (Figs. 13.18 and 13.19). A variable amount of mucin is usually present (Fig. 13.19). The histiocytes tend to infiltrate in between collagen bundles at the periphery of the granuloma giving rise to an interstitial pattern. "Interstitial granuloma annulare" is used to describe cases which demonstrate a prominent interstitial pattern in the absence of

palisading or necrobiosis (Fig. 13.20). There is usually a mild perivascular lymphocytic infiltrate with or without a few admixed eosinophils.

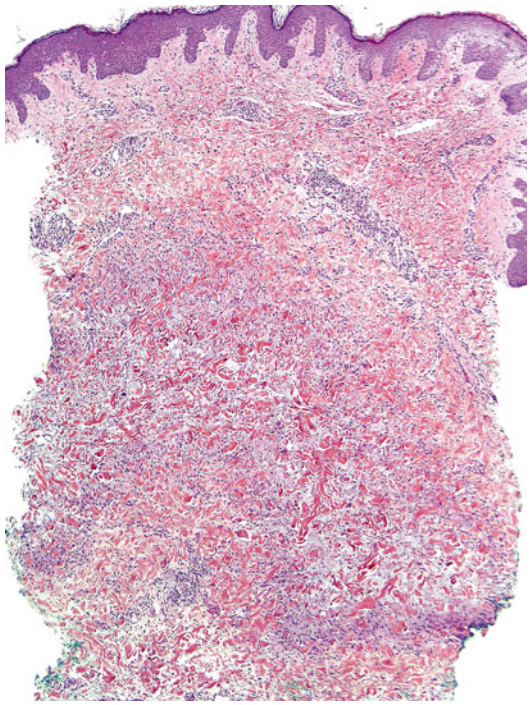

Fig. 13.17 Granuloma annulare. An annular infiltrate is present in the dermis

Sometimes a vaguely annular distribution of a mild perivascular lymphohistiocytic infiltrate may be the only clue to an early granuloma annulare. On rare occasions the lymphocytic infiltrate may be so brisk that it mimics a T-cell lymphoma (see section "Differential diagnosis" below) (Cota et al. 2012). Vascular changes including leukocytoclastic or granulomatous vasculitis and/or thrombogenic vasculopathy are found to be a marker for underlying systemic diseases (Magro et al. 1996). Cases associated with systemic diseases are also more likely to contain scattered extravascular neutrophils (Magro et al. 1996). Such cases are virtually indistinguishable from "interstitial granulomatous dermatitis" (Peroni et al. 2012) and "palisaded and neutrophilic granulomatous dermatitis" on histologic grounds (Chu et al. 1994).

In the perforating form, a well-developed palisading granuloma comes in direct contact with the overlying invaginated epidermis which has a disrupted basal layer. This forms a perforating channel permitting transepidermal elimination of the necrobiotic collagen (Fig. 13.21). Subcutaneous granuloma annulare is characterized by numerous palisading granulomas located primarily within the subcutaneous fat, with or without involvement of the overlying dermis (Fig. 13.22).

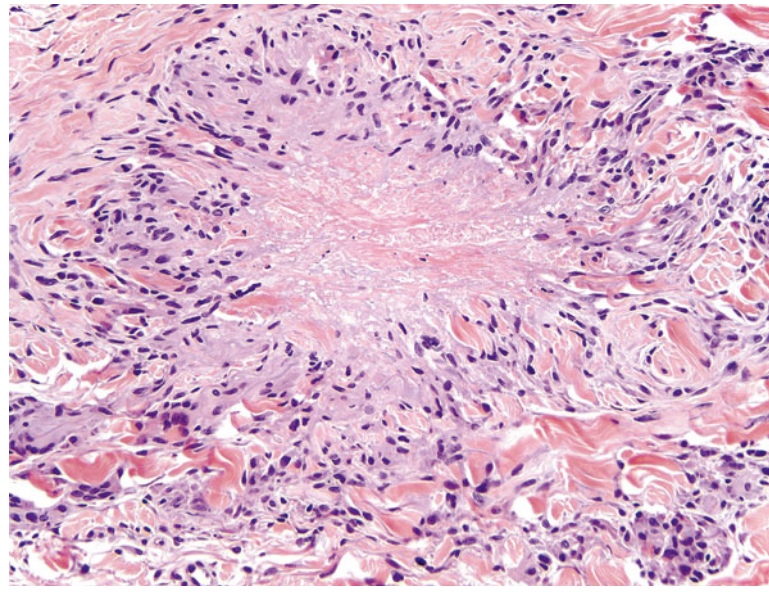

Fig. 13.18 Granuloma annulare. Spindle-shaped histiocytes palisade around a central zone of necrobiosis composed of swollen and degenerated collagen

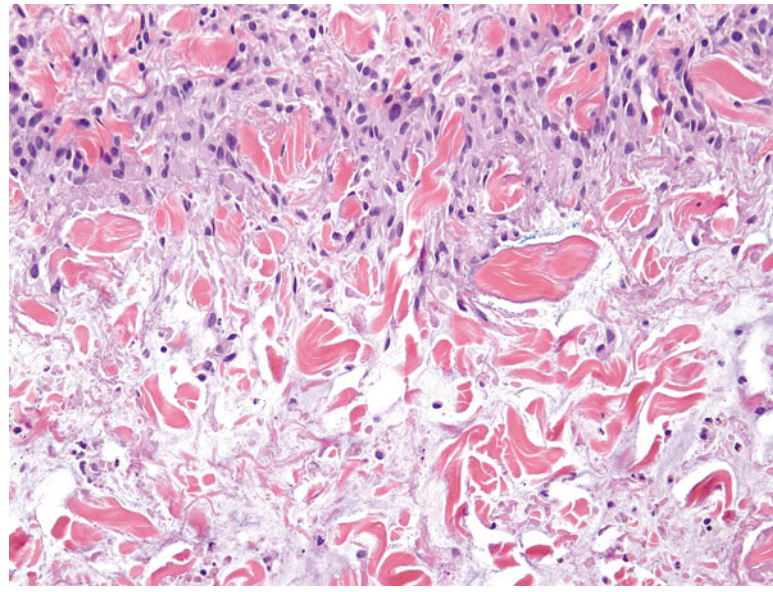

Fig. 13.19 Granuloma annulare. The central necrobiotic zone consists of fragmented collagen and abundant mucin

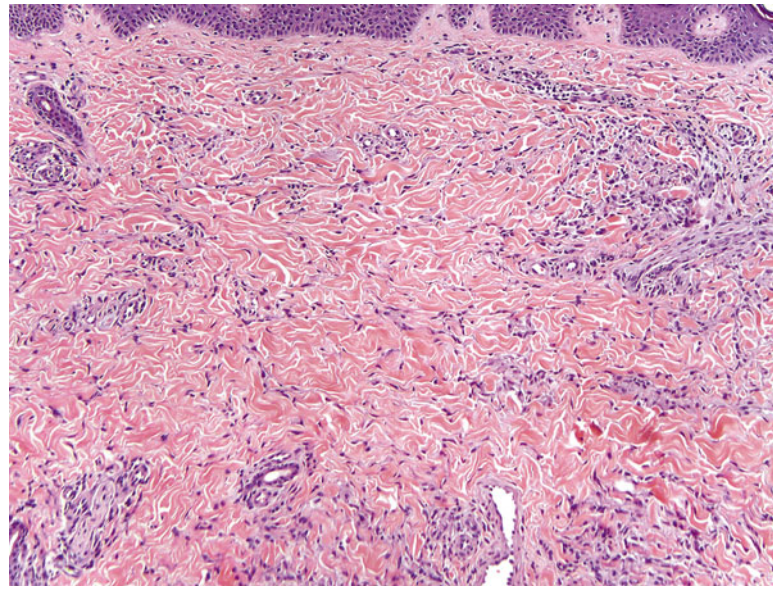

Fig. 13.20 Interstitial granuloma annulare. In this example the histiocytes percolate between collagen bundles without palisading around a central necrobiotic zone. A mild perivascular lymphocytic infiltrate is also present

Immunophenotype

The histiocytes in granuloma annulare are immunoreactive for CD68 and CD163. Staining for lysozyme is variable (Stefanaki et al. 2007). The lymphocytic infiltrate is comprised of mostly T cells, with CD4 predominating over CD8 in most cases except in those associated with immunodeficiency (Morris et al. 2002; Stefanaki et al. 2007).

Genetics and Molecular Findings

A study has found clonal T cells in 2 of 15 cases (13 %) of granuloma annulare by T-cell receptor (TCR) gene rearrangement analysis (Pfaltz et al. 2011). Another study has detected T-cell clonality in 3 of 12 cases (25 %), but the clone was only demonstrable in one of the two biopsies obtained from the same patients (Dabiri et al. 2011).

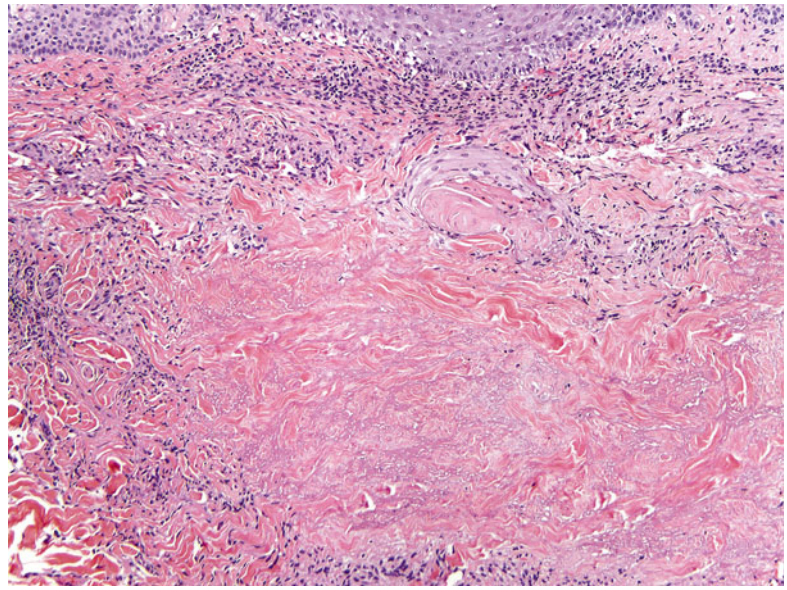

Fig. 13.21 Perforating granuloma annulare. The palisading granuloma comes in direct contact with the invaginated epidermis, forming a perforating channel in the process of transepidermal elimination of the necrobiotic collagen

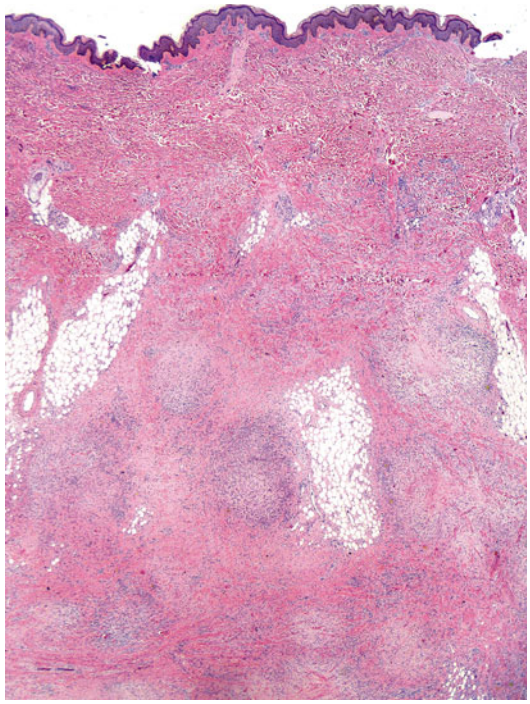

Fig. 13.22 Subcutaneous granuloma annulare. Numerous palisading granulomas are present exclusively in the subcutaneous tissue

This "dual TCR-PCR" approach supports a false-positive result in some cases of granuloma annulare and is helpful in distinguishing these cases from granulomatous T-cell lymphoma.

Prognosis and Course

More than half of the cases resolve spontaneously within 2 years of onset (Zax and Callen 1990; Dahl 1993). Recurrence at the same sites is not uncommon. The generalized form may result in anetoderma (Ozkan et al. 2000; Kiremitci et al. 2006). The possible role of biopsy in promoting resolution of granuloma annulare remains controversial (Levin et al. 2002; Wells and Smith 1963).

Differential Diagnosis

Necrobiosis lipoidica is another palisading granulomatous dermatitis which may be difficult to distinguish from granuloma annulare. Clinically, the classic presentation of an orange plaque on the shin favors necrobiosis lipoidica. The granulomas in necrobiosis lipoidica tend to be organized horizontally resulting in a "layered" appearance. There is usually more extensive and prominent eosinophilic necrobiosis than in granuloma annulare. Other findings in favor of necrobiosis lipoidica include a conspicuous plasma cell infiltrate, the lack of an interstitial pattern, and the paucity of mucin.

Cutaneous infections caused by certain organisms, such as *Mycobacterium marinum* and *Borrelia burgdorferi*, may elicit an interstitial

granulomatous dermatitis simulating interstitial granuloma annulare (Barr et al. 2003; Moreno et al. 2003). Borrelial infection may demonstrate "histiocytic pseudorosettes." Work-up for an infectious cause should be considered in patients with atypical clinical presentations and/or under immunosuppression.

Mycosis fungoides (MF) may contain a reactive granulomatous component in addition to the neoplastic lymphocytic infiltrate (LeBoit et al. 1988). In particular, interstitial MF is a rare variant in which the prominent interstitial distribution of the infiltrate closely mimics that of interstitial granuloma annulare (Su et al. 2002). While some of these cases may be recognized histologically based on the findings of epidermotropism and lymphocytic atypia, others may require molecular analysis to confirm a neoplastic T-cell clone. A study suggested the presence of pseudovascular clefts with "free-floating" collagen fibers as a helpful clue in identifying interstitial MF (Ferrara et al. 2010). Of note, interstitial granuloma annulare may be seen in association with mycosis fungoides, which further adds to the diagnostic challenge (Koochek et al. 2012).

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