Nodular B-Lymphocyte Reactive Patterns: Reactive Nodular B-Cell Pattern

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Introduction

Overview of B-Lymphocyte Ontogeny

All B lymphocytes arise in the bone marrow from a stem cell. Once formed, B lymphocytes mature in the following stages: *a pro-B lymphocyte* followed by a pre-B lymphocyte (the earliest cell type to synthesize detectable Ig gene products such as the μ heavy chains), followed by the immature IgM-bearing B lymphocyte, followed by the mature antigen-responsive B lymphocyte which produces both membrane IgM and IgD, and followed by the activated B lymphocyte which proliferates and differentiates to produce immunoglobulin in a secreted form. All, except the last two stages, which are antigen-induced, are antigen-independent cells. Stem cells and pro-/pre-B lymphocytes are only seen in primary hematopoietic tissues (such as bone marrow and fetal liver), while immature as well as mature B lymphocytes are found in the bone marrow, peripheral blood, and secondary lymphoid organs. Activated and antibody-secreting B lymphocytes are predominantly seen in the peripheral blood and secondary lymphoid organs (Abbas et al. 1991).

Immunophenotypically, surface markers characterize each of these stages. Pro-B cells express the following immunomarkers: TdT, Pax-5, CD10, CD19, CD40, CD34, and MHC class II antigens; pre-B lymphocytes express TdT, CD79a, CD79b, Pax-5, CD10, CD19, CD40, CD34, CD43, and CD22; mature B lymphocytes express CD19, CD20, CD21, CD23, CD40, and MHC class II antigens (but no longer express TdT, CD10, and CD34) and activated B lymphocytes lose expression of sIgD and CD21 but express CD25, CD80, and CD86 (Fig. 7.1) (LeBien and Tedder 2008).

Historical Overview and Clarification of Nomenclature

Conceptually, the definition of pseudolymphoma is somewhat confusing as the term lacks specificity primarily because it does not provide clues about the etiopathogenesis. Confounding issues include the fact that identification of the antigenic stimulus may not be helpful as more often than not the "process" continues long after the initiating event. The term, coined initially to describe a process in the late 1800s, was used to denote an entity that had a banal clinical course but histopathologically mimicked lymphoma. Since its initial description, the process has been identified in several other organ systems such as the breast,

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H.D. Cualing et al. (eds.), *Cutaneous Hematopathology*,
DOI 10.1007/978-1-4939-0950-6_7,

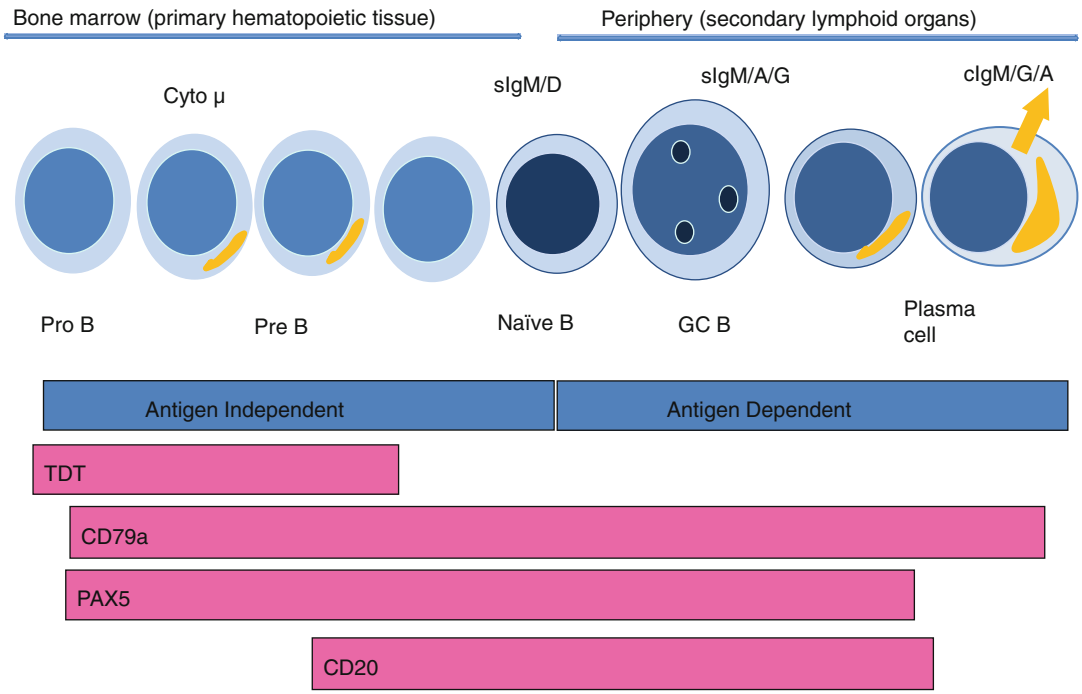

Fig. 7.1 Schematic overview of B-lymphocyte ontogeny

the gastrointestinal tract, the lung, the salivary and lacrimal gland, the skin, the soft tissue, and the thyroid gland. Cutaneous pseudolymphoma was first described as sarcomatosis cutis by Kaposi in 1891 (Bluefarb 1960). A couple of decades later in 1923, the term lymphocytoma cutis was coined by Biberstein (Kerl and Ackerman 1993). In subsequent years, other terms such as lymphadenosis benigna cutis by Bafverstedt in 1943, pseudolymphoma of Spiegler and Fendt introduced by Lever in 1967 (Kerl and Ackerman 1993), cutaneous lymphoid hyperplasia (Caro and Helwig 1969), and cutaneous B-cell pseudolymphomas (CBPL) (Caro and Helwig 1969; Evans et al. 1979) were used to denote an entity with similar if not identical histopathology features.

Prior to the availability of immunophenotyping techniques and immunoglobulin and polymerase chain reaction (PCR) gene rearrangement analyses, the diagnosis of cutaneous pseudolymphoma (CPL) was based primarily on clinicopathologic correlation (Caro and Helwig 1969; Evans et al. 1979). Confirmation of the diagnosis of CPL was based on absence of systemic involvement 5 years from the date of the original biopsy (Caro and Helwig 1969; Ploysangam et al. 1998; Rijlaarsdam and Willemze 1994).

Histopathologic Overview of Reaction Pattern/s

In a normal lymph node, the cortex is the location of primary and secondary lymphoid follicles. In the absence of immune stimulation, the cortical lymphoid follicles are primary follicles, composed of small B lymphocytes, which may be virgin B lymphocytes or recirculating memory B lymphocytes. There is also a fine meshwork of reticulum cells, usually not visible without special immunolabeling techniques. With antigenic stimulation, antigen recognizing B lymphocytes are stimulated to replicate and differentiate – a process that converts the primary follicle into a secondary follicle or germinal center, surrounded by a mantle zone of transient small lymphocytes, and a central area containing replicating "follicular center cells"

and their differentiating progeny (centroblasts and centrocytes). Normal germinal centers are characterized by the presence of tingible body macrophages, a well-formed mantle zone peripherally, normal polarization (darker-staining cells dominating the deeper half of the germinal center), and an increased proliferation index.

Reactive cutaneous lymphoid hyperplasia is characterized by lymphoid follicles with a poorly formed or absent mantle zone. Follicle centers in reactive lymphoid hyperplasia may still maintain polarization and have obvious tingible body macrophages and more centroblasts and immunoblasts than the normal follicle. There are four characteristic histologic patterns of reactive lymphoid hyperplasia (CLH): germinal center (GC) cell clusters forming well-defined lymphoid follicles, GC cell clusters not forming well-defined lymphoid follicles, CLH with a prominent histiocytic component, and CLH with a nonspecific mixed T and B lymphocytes (Bergman et al. 2011).

Classification

Currently, classification of cutaneous pseudolymphoma (CPL) is based on the histopathologic features and results of immunophenotyping and genotyping of the lymphocytes (Rijlaarsdam and Willemze 1994). Cutaneous pseudolymphoma consists of two major subtypes based on the predominant lymphocytes in the infiltrate: (1) cutaneous T-cell pseudolymphomas (CTPL) and (2) cutaneous B-cell pseudolymphomas (CBPL).

Epidemiology

Although it may occur at any age, CBPL characteristically develops in early adult life, with a median age of 34 years (range 1–73 years) (Caro and Helwig 1969). Approximately two-thirds of patients typically present initially below the age of 40 (Ploysangam et al. 1998). The female to male ratio is 3:1 (Brodell and Santa Cruz 1985) with predominance in Caucasians (white to black = 9:1) (Caro and Helwig 1969; Ploysangam et al. 1998). To date, no familial cases have been reported. While no definite geographic distribution has been identified, CBPL associated with infectious organisms (e.g., *Borrelia burgdorferi*) commonly occurs in endemic regions of the specific infection. The most common sites of involvement include the face (cheek, nose, and ear lobe; 70 %), chest/nipples (36 %), and upper extremities (25 %) (Brodell and Santa Cruz 1985; Caro and Helwig 1969; Kerl and Ackerman 1993; Rijlaarsdam and Willemze 1994).

Etiology

The most common cause of cutaneous nodular reactive B-lymphocyte hyperplasia (cutaneous B-cell pseudolymphoma) is idiopathic. The remaining causes arranged in order of decreasing frequency based on a retrospective literature review of 32 years (1981 to present) include drugs, foreign body reaction, infection (in particular with *Borrelia burgdorferi*, *Treponema pallidum* and herpes simplex virus types 1 and 2, and varicella zoster virus) vaccination, and arthropod assault. Nomenclature based on varied etiopathogenesis includes idiopathic lymphocytoma cutis, persistent nodular arthropod-bite reactions, tattoo-induced lymphocytoma cutis (secondary to a foreign body reaction), lymphocytoma cutis caused by injections/acupuncture (vaccination), lymphomatoid drug-induced pseudo B-cell lymphoma, infectious lymphocytoma cutis (secondary to infection with *Borrelia burgdorferi*, *Treponema pallidum*, herpes simplex virus types 1 and 2, and Varicella zoster virus) and acral pseudolymphomatous angiokeratoma (of unknown etiology) (Crowson and Magro 1995; Kerl and Ackerman 1993; Ploysangam et al. 1998; Rijlaarsdam and Willemze 1994).

Idiopathic Lymphocytoma Cutis

Definition

Idiopathic lymphocytoma cutis, a benign B-cell predominant lymphoproliferative disorder of unknown etiology, is the prototypic example of CBPL.

Clinical Features

Clinically, two distinct forms have been reported: a more common localized form (comprising approximately 72 %) (Brodell and Santa Cruz 1985; Caro and Helwig 1969; Kerl and Ackerman 1993; Rijlaarsdam and Willemze 1994) and a less frequent generalized form (Brodell and Santa Cruz 1985; Gartman 1986; Kerl 1983; Moreno et al. 1991; Self et al. 1969). The former usually presents as a single asymptomatic nodule or tumor of variable consistency, measuring up to 4 cm in diameter. Lesions may be aggregated in small clusters with a few millimeter-sized miliary papules. The color varies from skin-colored to red brown/purple. Scale and ulceration are generally absent (Ploysangam et al. 1998). There is typically no extracutaneous involvement, but local recurrence has been reported (Ploysangam et al. 1998).

Histopathology

Histopathologic features include a dense, superficial, and mid-dermal nodular infiltrate of lymphocytes admixed with a variable number of histiocytes, eosinophils, and plasma cells (Fig. 7.2a). While the infiltrate is typically present predominantly in the papillary dermis ("top-heavy" pattern) (Ackerman 1978; Ackerman et al. 1993; Clark et al. 1974; Connors and Ackerman 1976; Friedmann 1990; Lever et al. 1990; MacKie 1993; Rijlaarsdam et al. 1990; Van Hale and Winkelmann 1985), a few cases of CBPL in which the infiltrate extends into the subcutis and/or in a diffuse pattern have been reported. Two types of nodular infiltrate may be seen: a small-cell variant with a more typical central germinal center that lacks cellular pleomorphism (Fig. 7.2b–d) and a large-cell vari-

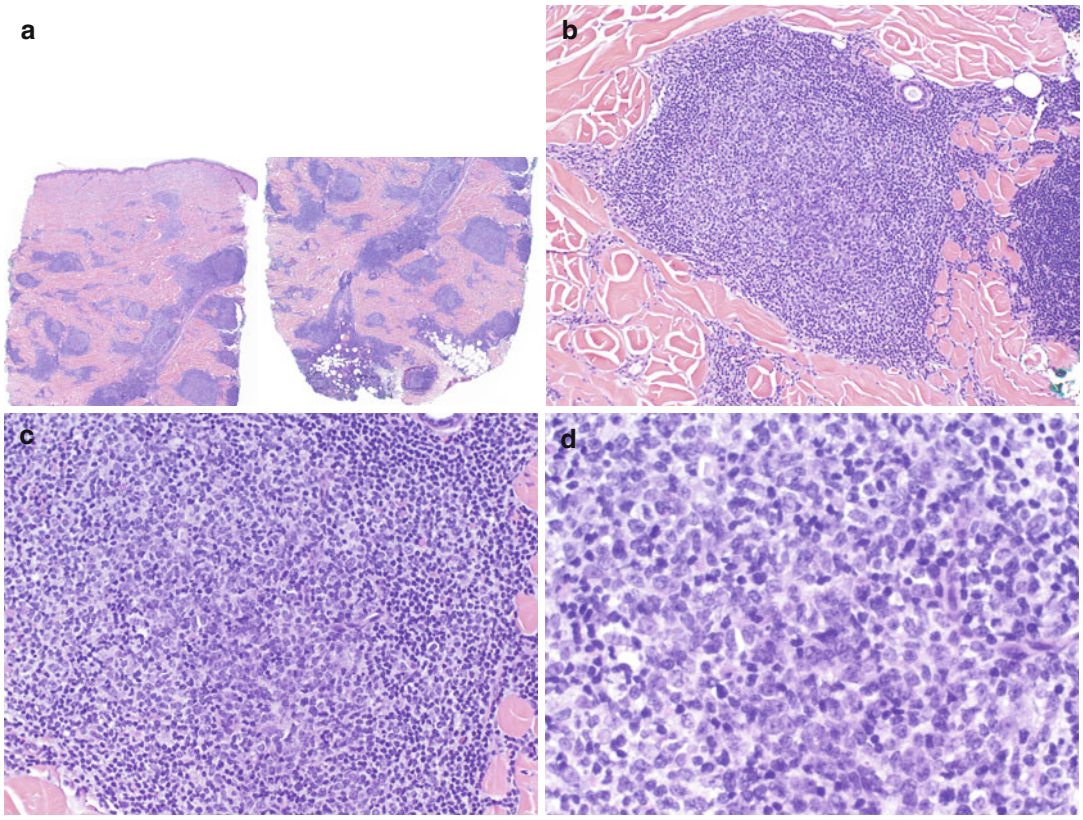

Fig. 7.2 (**a**–**d**) Prototypic reactive cutaneous B-cell nodular lymphoid hyperplasia (H&E). (**a**) Scanning magnification; (**a1**); upper half, (**a2**); lower half, (**b**) reactive follicle, (**c**) regular germinal center with mantle zone, (**d**) germinal center with polymorphic infiltrate of centrocytes, centroblasts, immunoblasts, and macrophages with tingible bodies

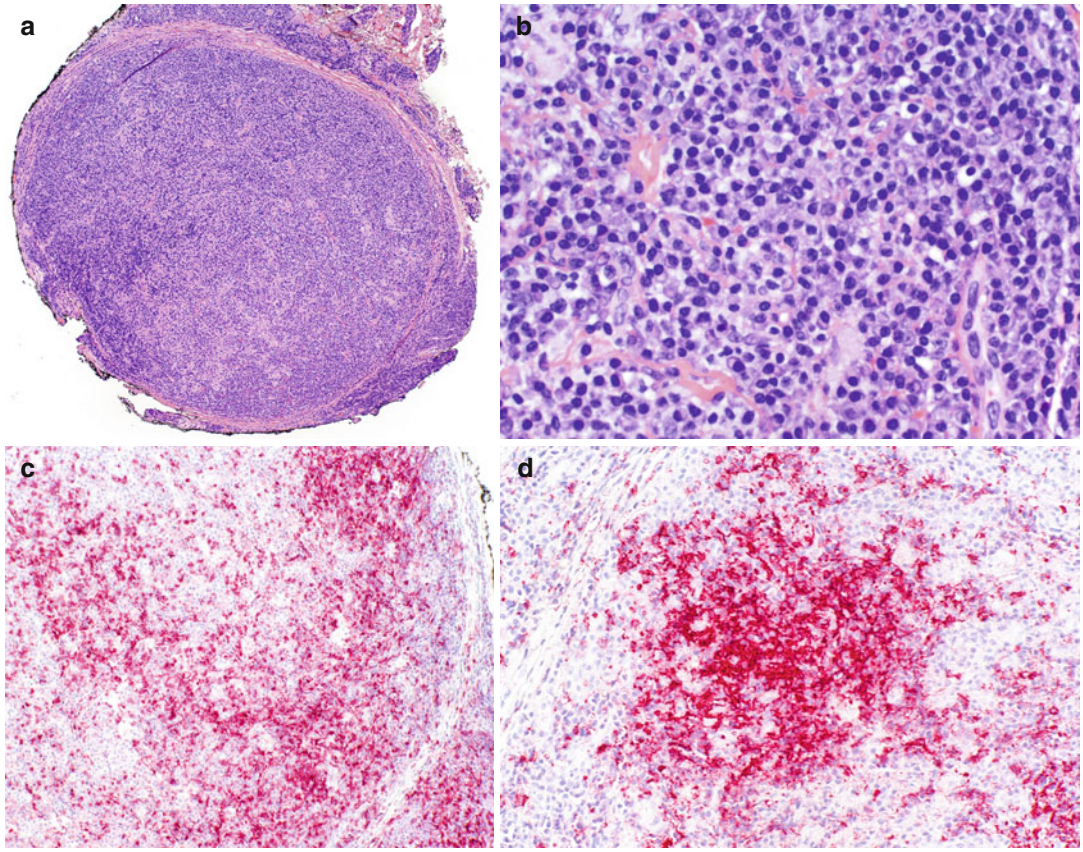

Fig. 7.3 (**a**–**d**) Plasma cell predominant reactive cutaneous B-cell nodular lymphoid hyperplasia. (**a**) H&E, scanning magnification; (**b**) H&E, plasma cell-rich infiltrate, (**c**) CD3, (**d**) CD20

ant that has large pleomorphic lymphocytes mainly in the central part of the infiltrate. The latter can be difficult to distinguish from lymphoma (Brodell and Santa Cruz 1985). Other cell types that may be found in germinal centers are T-helper lymphocytes, macrophages with tingible bodies, and regular patterned (highlighted by CD21) follicular dendritic cells (Ackerman 1978; Ackerman et al. 1993; Connors and Ackerman 1976; Friedmann 1990; Lever and Schaumburg-Lever 1990; MacKie 1993; Rijlaarsdam et al. 1990; Van Hale and Winkelmann 1985). In rare instances, plasma cells may be the predominant cell type (so-called primary cutaneous plasmacytoma/plasma cell predominant CBPL) (Fig. 7.3a–d) (Brodell and Santa Cruz 1985; Hurt and Santa Cruz 1990; Kerl and Ackerman 1993). A rare histopathology subset of CBPL is "large-cell lymphocytoma" (Duncan et al. 1980; English et al. 1986; Winkelmann and Dabski 1987) – a variant that can be difficult to differentiate from CBCLs. In the nine cases reported by Duncan et al. (1980; English et al. 1986; Winkelmann and Dabski 1987), seven ended up with a diagnosis of lymphoma. In a similar report of 14 "large-cell lymphocytoma" cases, a diagnosis of lymphoma was made initially, but long-term follow-up showed a benign course (English et al. 1989). These cases, with apparent contradictory clinical courses, were histopathologically described by Winkelmann's group as showing "sharply marginated, dense clusters of small lymphocytes surrounded or infiltrated the large cell component, a juxtaposition that characterizes large cell lymphocytoma" (Winkelmann and Dabski 1987).

Immunophenotype

Immunohistochemical stains reveal a normal phenotype of the germinal center cells (CD20+, CD79a, CD10+, Bcl6+, Bcl2-) (Ploysangam et al. 1998) (Fig. 7.4a–d), normal high proliferation MIB-1/Ki67, with polytypic expression of immunoglobulin light chain. A regular and sharply demarcated network of follicular dendritic cells is highlighted by using CD21 or CD35. A prominent population of reactive CD3+ T lymphocytes is always present admixed with the infiltrate especially at the periphery (Fig. 7.4e).

Cytogenetics and Molecular Findings

In most cases, polyclonality is observed in gene rearrangement of immunoglobulin heavy-chain genes (Leinweber et al. 2004). In addition, there is no light-chain restriction of plasma cells. Of note, several studies have shown clonal gene rearrangement in morphologically reactive lymphoid hyperplasia. These include heavy-chain gene rearrangement detected in 5/14 cases (35 %) in the study by Wood et al., in 2/26 cases (7.7 %) in the study by Hammer et al., in 35/53 cases (66 %) in the study by Bouloc et al., in 27/44 cases (61 %) in the study by Nihal et al., in 1/10 cases (10 %) in the study by Leinweber et al., in 4/30 cases (13 %) in the study by Böer et al. 2008, and more recently in 3/24 cases (13 %) in the study by Bergman et al. 2011. The striking high prevalence of dominant clones in these series may have been the result of a selection bias encountered in a highly specialized referral centers for cutaneous lymphoma. Despite these high numbers, however, only a minority (<10 %) of cases of CBPL with a clonal population of B lymphocytes progressed to cutaneous lymphoma (Nihal et al. 2003).

Clinical Course

Given the fact that the cause is unknown, the clinical course varies considerably, but more often than not tends to be chronic and indolent (Brodell and Santa Cruz 1985; Kerl and Ackerman 1993;

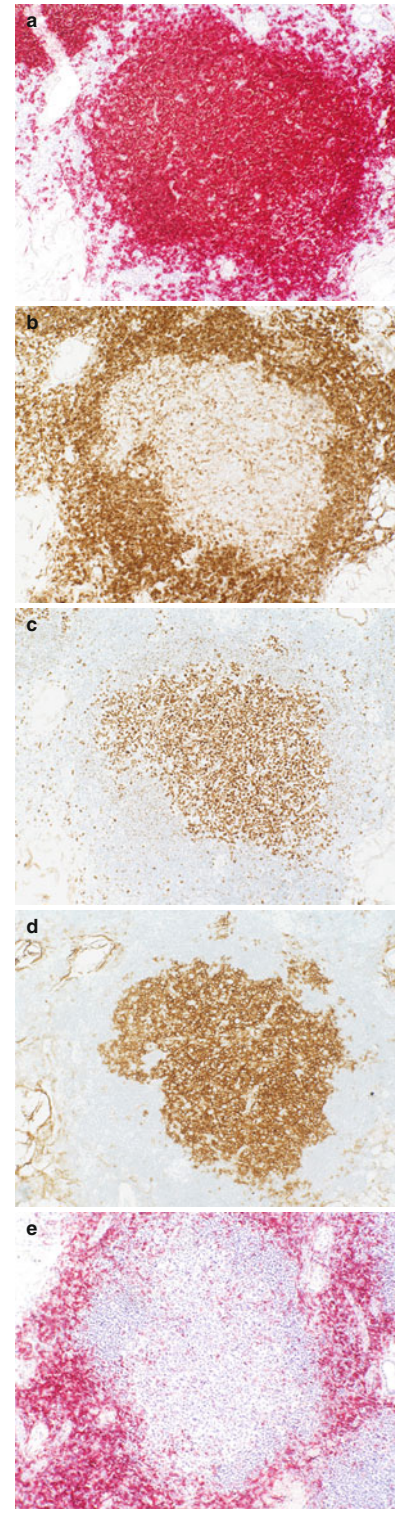

Fig. 7.4 (**a**–**e**) Typical immunohistochemical staining pattern of a reactive follicle. (**a**) CD20, (**b**) BCL2, (**c**) BCL6, (**d**) CD10, (**e**) CD3

Rijlaarsdam and Willemze 1994). Spontaneous regression may be seen in some lesions after several months or a few years, although local recurrence after prolonged periods has been reported in select cases (Brodell and Santa Cruz 1985; Kerl and Ackerman 1993; Rijlaarsdam and Willemze 1994).

Differential Diagnosis

Differential diagnoses include follicle-center lymphoma, marginal zone B-cell lymphoma, and diffuse large B-cell lymphoma. Helpful features in differentiating a benign from a malignant process include clinical presentation (small, localized lesion in the former vs. large, ulcerated and/or generalized lesions in the latter) (Brodell and Santa Cruz 1985; Kerl and Ackerman 1993; Rijlaarsdam and Willemze 1994), clinical course (spontaneous remission in the former vs. progressive course in the latter) (Brodell and Santa Cruz 1985; Rijlaarsdam and Willemze 1994), light-chain expression (polytypic in the former vs. monotypic in the latter), Bcl2 protein expression within germinal centers (relatively rare in the former vs. expression in 20–58 % of cases in the latter), and immunoglobulin chain gene rearrangements (positive in up to 28 % of cases of the former vs. 75 % of cases the latter) (Ploysangam et al. 1998).

Confounding clinical features include reported cases of primary CBCL without systemic involvement (Berti et al. 1991; Burg et al. 1994; Friedmann et al. 1995; Giannotti and Santucci 1993; Rijlaarsdam et al. 1993; Santucci et al. 1991; van der Putte et al. 1985), primary CBCL with features similar to that of CBPL such as clinical appearance (red- to plum-colored nodules), absence of extracutaneous involvement, response to local treatment, and a favorable prognosis. Thus, differentiating primary CBCL from CBPL on the basis of clinical evaluation alone can sometimes be a problem.

In cases with an atypical diffuse infiltrate, the most helpful differentiating feature is the presence of B lymphocytes with polyclonal light chains in CBPL, in contrast to CBCL in which there is predominance of one light chain (Halevy and Sandbank 1987; Wantzin et al. 1988). Light-chain restriction is valuable diagnostically only when the kappa to lambda ratios >10:1 or are <0.5:1 (LeBoit et al. 1994). Bcl2 are also useful in distinguishing primary cutaneous follicular lymphomas (follicular CBCL) from CBPL with germinal centers (Chimenti et al. 1996). Of note, positivity with the Bcl2 protein antibody has rarely been found in CBPL within germinal centers (Triscott et al. 1995).

In some subtypes of cutaneous lymphoma, such as the T-lymphocyte-rich CBCL, reactive benign small T lymphocytes can comprise a fairly sizeable population of the infiltrate. This can lead to misdiagnosis on the basis of immunohistochemical studies alone (Cerroni and Kerl 1994). In cases with a discrepancy between the clinical, histologic, and immunohistochemical studies, a search for gene rearrangements in both T and B lymphocytes is useful. Generally, benign or reactive processes are polyclonal, whereas the presence of monoclonality directs a malignant process. However, this distinction is not absolute because monoclonality has been demonstrated in some benign or reactive cutaneous lymphoid hyperplasia (Wechsler et al. 1990; Weinberg et al. 1993).

Lymphomatoid Drug-Induced Pseudo B-Cell Lymphoma

Definition

Lymphomatoid drug-induced pseudo B-cell lymphoma is a subtype of lymphomatoid drug eruptions. The spectrum of drugs reported to induce cutaneous lymphoid infiltrates include anticonvulsants, antipsychotics, antihypertensives (angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers, and diuretics), cytotoxics (cyclosporine, methotrexate, adalimumab, infliximab), antirheumatics (gold, salicylates, phenacetin, D-penicillamine, allopurinol, nonsteroidal antiinflammatory drugs), antibiotics (penicillin, dapsone, nitrofurantoin), antidepressants (fluoxetine, doxepin, desipramine, amitriptyline hydrochloride, lithium), anxiolytics (benzodiazepines), antihistamines (diphenhydramine), H2-antagonists (cimetidine,

ranitidine), antiarrhythmics (mexiletine chloride, procainamide), topical agents (menthol, etheric plant oil), sex steroids, lipid-lowering agent (lovastatin), and anti-TNF-α (Imafuku et al. 2012; Kerl and Ackerman 1993; Ploysangam et al. 1998; Rijlaarsdam and Willemze 1994; Sawada et al. 2010; Schmutz and Trechot 2012). Although most cases of lymphomatoid drug eruptions are reportedly of the CTPL type, a few CBPL cases have been reported in association with select drugs that include antihistamines, antidepressants, neuroleptics, and allopurinol (Aguilar et al. 1992; Crowson and Magro 1995; Magro and Crowson 1995; Paley et al. 2006; Torne et al. 1989). A rare type of lymphomatoid drug eruption with numerous CD30+ cells may simulate the CD30+ cutaneous lymphoproliferative disorders (Nathan and Belsito 1998). Of note, the same drug may present with varied skin lesions not only clinically but also with varying histopathology and phenotypic features in different patients.

While the precise etiopathogenesis of lymphomatoid drug eruptions is unknown, possible mechanisms postulated include impaired immunosurveillance by the offending agent which in turn leads to abnormal proliferation of lymphocytes and impairs the ability of cytotoxic/suppressor T lymphocytes to suppress B-lymphocyte differentiation and immunoglobulin production (Behan et al. 1976; Bluming et al. 1976; Brandes et al. 1992; Crowson and Magro 1995; Damle and Gupta 1981; Dosch et al. 1982; Magro and Crowson 1995; McMillen et al. 1985). Precise data concerning the incidence, prevalence, and geographic distribution of a lymphomatoid drug-induced pseudo B-cell lymphoma do not exist; however, anticonvulsant drugs, in particular phenytoin, cause pseudolymphoma syndrome with an increased frequency in African-American patients.

Clinical Features

Clinically, this variant may present as localized or generalized papules, plaques, nodules, or erythroderma (Ploysangam et al. 1998) with accentuation of cutaneous changes in sun-exposed areas. Anticonvulsant drugs, particularly hydantoin, induce the pseudolymphoma syndrome within the first 2–8 weeks of drug intake, but can occur from 5 days to 5 years after initiation of phenytoin therapy. Clinically, this syndrome is characterized by the triad of fever, lymphadenopathy, and an erythematous eruption (pruritic macules, papules and nodules) in association with eosinophilia, hepatosplenomegaly, leukocytosis, malaise, arthralgia, and severe edema of the face (Choi et al. 2003; Schreiber and McGregor 1968).

Histopathology

Cutaneous lesions usually show the band-like CTPL pattern mimicking MF. However, some cases of lymphomatoid drug eruptions may have the nodular CBPL pattern mimicking non-Hodgkin's lymphoma (Aguilar et al. 1992; Crowson and Magro 1995; Dorfman and Warnke 1974; Kardaun et al. 1988) or lymphocytoma cutis pattern with formation of reactive germinal centers. Eosinophils may or may not be present.

Immunophenotype

The cells in the central portion of the nodular infiltrate express the phenotype of mature lymphocytes (CD20 and CD79a) with a regular follicular dendritic cell pattern highlighted by CD21 and/or CD35. A prominent population of reactive CD3+ T lymphocytes admixed within and/or at the periphery of the B-cell-rich infiltrate is always present.

Cytogenetics and Molecular Findings

There is no immunoglobulin heavy-chain gene rearrangement and no light-chain restriction of plasma cells.

Clinical Course

Characteristically, the lesions disappear after discontinuing of the offending drugs.

Differential Diagnosis

The main differential diagnoses of lymphomatoid drug eruptions include cutaneous T-cell lymphoma, CTCL (mycoses fungoides, Sezary syndrome), CBCL (follicle-center lymphoma or marginal zone B-cell lymphoma) (Aguilar et al. 1992; Crowson and Magro 1995; Magro and Crowson 1995; Paley et al. 2006; Torne et al. 1989), and systemic lymphoma (non-Hodgkin's lymphoma) (Aguilar et al. 1992; Crowson and Magro 1995; Dorfman and Warnke 1974; Kardaun et al. 1988). In addition, in the type of lymphomatoid drug eruption with numerous CD30+ cells, CD30+ cutaneous lymphoproliferative disorders should be considered (Nathan and Belsito 1998). A case of CBCL arising in the fluoxetine-induced CBPL area has been reported in 2006. Therefore, follow-up is essential. Features favoring a reactive process are the same as those mentioned before in the section of differential diagnosis in an idiopathic lymphocytoma cutis.

Cutaneous Lymphoid Hyperplasia Secondary to Foreign Bodies: Reaction to Tattoo

Definition

Cutaneous pseudolymphoma is an unusual immune response that can be caused by various foreign materials such as metals in metal ear piercing and tattoos in particular cinnabar in lesions utilizing a red dye. Cutaneous pseudolymphoma due to tattoo occurs mainly in areas with red pigment (mainly cinnabar), but pseudolymphoma secondary to the blue dye (composed mainly of cobalt salts) and green dye (composed mainly of chrome salts) areas have also been described (Blumental et al. 1982). The precise underlying mechanism in the development of pseudolymphoma in a tattoo is still unclear although a delayed-type inflammatory reaction has been implicated (Lubach and Hinz 1986; Rijlaarsdam et al. 1988; Sanchez-Viera et al. 1992). Despite the popularity of tattooing and its high prevalence rate in adults (8.5 %) (Kazandjieva and Tsankov 2007), adverse inflammatory reactions to tattoo pigments are relatively infrequent (Stirn et al. 2006). The time of onset ranges from a few months up to 32 years after administration of the tattoo (Kahofer et al. 2003). In one report of two cases, different histologic reactions are reportedly associated with each dye, a lichenoid dermatitis resulting from a reaction to the red pigment, a pseudolymphoma resulting from a reaction to red and lilac pigments, and a photo-induced reaction to a yellow pigment (Cruz et al. 2010).

Clinical Features

Clinically, it typically presents as an asymptomatic red-discolored plaque to nodule limited to areas impregnated with the offending agent. Itching has occasionally been observed in some patients (Blumental et al. 1982; Kahofer et al. 2003; Rijlaarsdam et al. 1988).

Histopathology

Histopathologically, reactions to tattoos are diverse and include spongiotic, lichenoid, granulomatous, and a pseudolymphomatous reaction patterns (Kazandjieva and Tsankov 2007). Of note, granulomatous tattoo reactions, which usually represent hypersensitivity reactions to tattoo pigments, have been reported as a manifestation of systemic sarcoidosis in patients with a known history of the same (i.e sarcoidosis) (Sowden et al. 1992). Granulomatous dermatitis in a tattoo area may also develop in association with other manifestation of sarcoidosis (Sowden et al. 1992).

The pseudolymphomatous reaction pattern comprises a dense, diffuse lymphohistiocytic ("top-heavy" distribution) infiltrate with some eosinophils and occasionally plasma cells interspersed with dark brown, granular, non-refractile foreign body material (more often seen at the bottom of the infiltrate) within the cytoplasm of histiocytes as well as extracellularly between collagen bundles (Fig. 7.5) (Kahofer et al. 2003). The cytomorphology of lesional lymphocytes indicates that they are small. Follicular and nodular structures

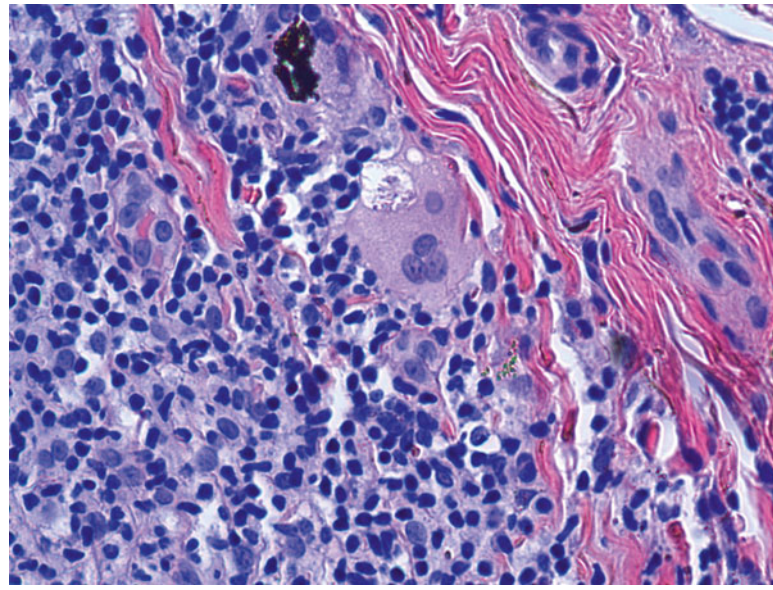

Fig. 7.5 Reactive cutaneous B-cell nodular lymphoid hyperplasia secondary to a foreign body (tattoo) H&E, nodular lymphohistiocytic infiltrate with admixed black, granular non-refractile foreign material consistent with tattoo

have occasionally been encountered. Rijlaarsdam et al. suggest that there is a follicle-center cell reaction pattern to tattoo pigment with distinct B- and T-lymphocyte compartments, simulating reactive lymph nodes (Rijlaarsdam et al. 1988). Overlying epidermal change in the form of parakeratosis and irregular epidermal hyperplasia with scattered necrotic keratinocytes may be seen.

Immunophenotype

The cells of CBPL express the phenotypes of mature lymphocytes (CD20 and CD79a+) admixed with a prominent population of reactive CD3+ T lymphocytes and polyclonal plasma cells. Antigen-presenting CD1a + Langerhans cells are noted in the T-cell compartment, while CD21+ follicular dendritic cells appear to be confined to the B-cell compartment.

Cytogenetics and Molecular Findings

No heavy-chain gene rearrangement of immunoglobulin heavy-chain genes is present, and there is no light-chain restriction of plasma cells.

Clinical Course

While the lesions generally resolve after nonaggressive treatment, they have been known to persist for months with or without treatment.

Differential Diagnosis

The main differential diagnosis of pseudolymphomatous reactions to tattoo includes follicle-center lymphoma and marginal zone B-cell lymphoma. A case of CBCL arising in a tattoo has been reported. In this report, the patient initially presented with multiple pseudolymphomatous skin lesions, apparently associated with an immune response to the mercury contained in the red tattoo pigment. Over a period of 4 years, his skin lesions evolved from being histopathologically benign (mild-moderate, superficial and deep, predominantly perivascular lymphohistiocytic infiltrate with admixed plasma cells) and immunologically polyclonal pseudolymphoma to histopathologically malignant (dense, superficial and mid, nodular to diffuse infiltrate composed of large atypical lymphoid cells with admixed eosinophils and small lymphocytes) and immunologically

monoclonal large B-cell lymphoma indicating that follow-up is essential (Sangueza et al. 1992). In all biopsies, there were common clonal bands of varied intensity relative to the germline bands (reflecting a variability in the proportion of clonal cells) – finding favoring the concept of evolution from an abnormal immune state with multiple B-lymphocyte clones in the pseudolymphoma to a dominant and relatively uncontrollable proliferation of one clonal population in overt lymphoma (Breza et al. 2006).

Pseudo B-Cell Lymphoma Secondary to Infections

These include infections secondary to borreliosis, syphilis, and, albeit less commonly, herpes (as this typically causes CTPL per published reports).

Borreliosis

Definition

Borrelial lymphocytoma cutis is the most common cause of pseudo B-cell lymphoma particularly in endemic areas of Central Europe (Slovenia and Austria), Australia, and the Northeastern part of the United States (Connecticut). Other reported borreliosis cases are from northern Africa (Morocco, Algeria, Egypt, and Tunisia), Asia (Japan, northwest China, Nepal, Thailand, and far eastern Russia), Canada (Ontario), and South America (Brazil). In the United States, according to the CDC 2011 report, 96 % of cases were from the northeast and upper Midwest including Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Vermont, Virginia, and Wisconsin. This entity is a reactive B-lymphocyte predominant lymphoproliferative disorder caused by a tick bite with *B. burgdorferi*. The diagnosis is made by (1) a history of preceding erythema chronicum migrans or a tick bite, (2) clinical presentation of a blue-red nodule on the earlobe or on the nipple area, (3) histopathology features of lymphocytoma cutis, (4) elevated serum antibody titer to *B. burgdorferi*, and (5) identification of the organism in the tissue by polymerase chain reaction-based techniques (Asbrink and Hovmark 1993).

The prevalence of borrelial lymphocytoma cutis has been reported to be from 0.6 to 1.3 % (Stanek et al. 1985). It most commonly occurs in areas endemic for the Ixodes ricinus tick in Europe, also in North America as mentioned above (Hovmark et al. 1986). It is more common in women than men and may be seen in any age range including children (Colli et al. 2004; Hovmark et al. 1986).

Clinical Features

Clinically, borrelial lymphocytoma cutis often appears at the site of a tick bite or occurs close to the periphery of a large lesion of erythema chronicum migrans (Asbrink and Hovmark 1993). Most patients are aware of having had a tick bite. In comparison with erythema chronicum migrans, borrelial lymphocytoma cutis develops later and lasts longer. The incubation period varies from a few weeks to 10 months (Albrecht et al. 1991; Asbrink and Hovmark 1993; Bratzke et al. 1989; Bucher et al. 1988; Weber et al. 1984). Predilection sites include the earlobe, the nipple and areola, the nose, and the scrotal area (89 % of cases in one series) (Colli et al. 2004), indicating that spirochetes may prefer regions with low skin temperature. Borrelial lymphocytoma cutis usually has an asymptomatic blue-red plaque, papule, or nodule, varying in diameter from 3 mm to 5 cm or more (Wantzin et al. 1982). They may be solitary, grouped or numerous, and widespread (Zackheim et al. 1997).

Histopathology

The histopathologic appearances are varied and there is considerable overlap with primary cutaneous follicle-center cell lymphoma and primary cutaneous marginal zone B-cell lymphoma. There is a variably dense, nodular, mixed-cell infiltrate, which may have a perivascular and periappendageal distribution or be more diffuse (Fig. 7.6a, b). The epidermis is usually spared but some small lymphocytes may be seen traversing the entire epidermis. Although a

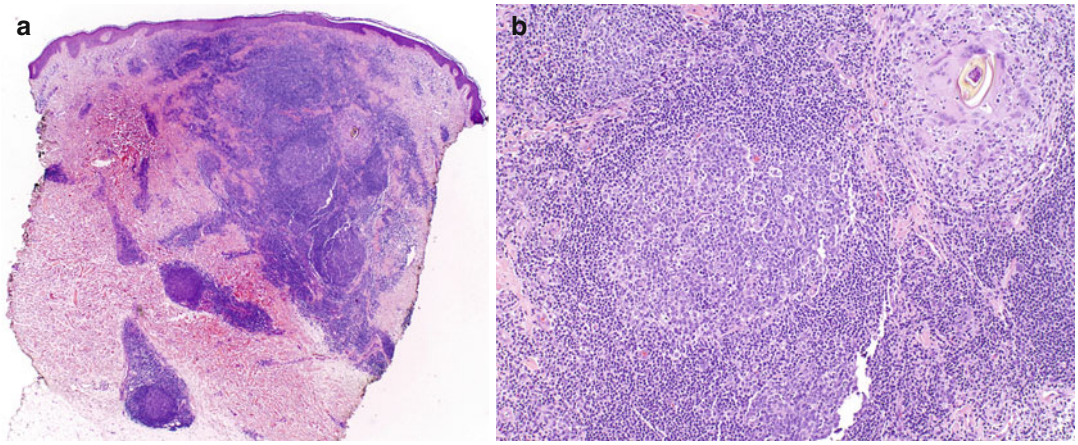

Fig. 7.6 (**a**, **b**) Reactive cutaneous B-cell nodular lymphoid hyperplasia secondary to a tick bite (**a**) H&E, scanning magnification, (**b**) H&E, reactive nodular lymphocytic infiltrate with germinal center formation (*left*), and a foreign body material reminiscent of part of a tick with an adjacent multinucleate giant cell reaction (*right upper*)

"top-heavy" cellular infiltrate is more typical, the infiltrate may extend into the subcutis. Lymphoid follicles are present in many but not all cases, and well-developed mantle zones are seen in a minority, which may present a difficulty in distinguishing reactive hyperplasia from follicle-center cell lymphoma. Plasma cells and eosinophils are found in almost all cases. However, the composition of follicles is different from that seen in follicle-center cell lymphoma. In CBPL, germinal centers were characterized by predominance of "blastic" cells with features of centroblasts, immunoblasts, and a relatively low number of centrocytes (Colli et al. 2004). Fusion of irregular follicle centers may simulate a pattern of diffuse large B-cell lymphoma (Grange et al. 2002). Presence of an intact or part of a tick argues in favor of a reactive process (Fig. 7.6b).

Immunophenotype

The infiltrate is composed mainly composed of CD10+ and Bcl2− germinal centers and polyclonal plasma cells. Dendritic cells positive for CD1a and S100 are also present in the infiltrate (Bergman et al. 2006).

Cytogenetics and Molecular Findings

Heavy-chain gene rearrangement is typically not seen and there is usually no light-chain restriction of plasma cells.

Clinical Course

If treatment is not given, the lesion may persist for several months with or without regional lymphadenopathy (Asbrink and Hovmark 1993). It has been reported that borrelial lymphocytoma cutis and acrodermatitis chronica atrophicans can be seen in the same patient (Asbrink and Hovmark 1993). Constitutional symptoms or other late manifestations of Lyme disease are found only in a few patients (Asbrink and Hovmark 1993). Serum antibodies to *B. burgdorferi* are elevated in 50 % of cases (Asbrink and Hovmark 1993). *B. burgdorferi* may rarely be the cause of systemic pseudolymphomatous syndrome that recedes after antibiotic treatment (Aigelsreiter et al. 2005).

Differential Diagnosis

The differential diagnoses of pseudolymphomatous reactions caused by *B. burgdorferi* include CBCL (follicle-center lymphoma or marginal zone B-cell lymphoma). Helpful differentiating features are the same as mentioned before under the section of differential diagnosis in an idiopathic lymphocytoma cutis.

Syphilis

Definition

According to the CDC 2010 report, the incidence of syphilis increased from 2001 to 2009 (total

primary and secondary cases, approximately 14,000) but started to decrease in 2010 (by 1.6 %). While the rate of congenital syphilis rate decreased by 15 % since 2008, rates remain high in some urban areas throughout the United States and in select rural areas (in the south). The co-occurrence of syphilis in human immunodeficiency virus (HIV)-positive homosexual men has further contributed to the increased incidence.

Overall, lesions of secondary syphilis characterized by a B-lymphocyte-rich infiltrate and widespread dissemination of spirochetes are still seen (Brown et al. 1999). A reactive B-lymphocyte predominant lymphoproliferative disorder secondary to infection *Treponema pallidum* is typically seen as a manifestation of secondary syphilis, although occasional cases (<25 reported cases in the literature) have been reported as a manifestation of late syphilis (Erfurt et al. 2006; McComb et al. 2003; Moon et al. 2009; ul Bari and Raza 2006).

Clinical Features

Secondary syphilis typically presents 2–6 months after inoculation with the spirochete *Treponema pallidum* (Abell et al. 1975). The classic presentation is that of a generalized papulosquamous/papulonodular eruption involving the skin and mucosa and accompanied by a flu-like prodrome with lymphadenopathy (Sanches 2003). The reddish-purple nodules and plaques, with/without peripheral scaling, are characteristically bilateral, symmetric, more prominent on the upper extremities and, albeit in the early stages, on the palms and soles (Sanches 2003). A case with the clinical presentation of infiltrated, erythematous to violaceous, coalescent plaques on the trunk, limbs, and face, giving an almost leonine facies simulating T- or B-cell lymphoproliferative disease, has been reported (Battistella et al. 2008).

Histopathology

The characteristic histopathology features of secondary syphilis include endarteritis, a superficial and deep, perivascular and perineural, lymphoplasmacytic infiltrate (although plasma cells may be absent or sparse in up to one-third of cases and vascular changes may not be prominent), an inflammatory cell infiltrate obscuring the dermoepidermal junction, and epidermal hyperplasia (lichenoid psoriasiform) with or without exocytosis (Jeerapaet and Ackerman 1974). The composition and depth of the infiltrate can vary from area to area even within a single biopsy. Few cases of secondary syphilis with a dense and diffuse dermal lymphocytic infiltrate have been reported to histologically mimic a lymphoid neoplasm (Cochran et al. 1976; Goffinet et al. 1970; Gollnick et al. 1987; Hodak et al. 1987).

Immunophenotype, Cytogenetics, and Molecular Findings

The plasma cells always reveal a polyclonal pattern of immunoglobulin light-chain expression, and immunohistologic staining for *Treponema pallidum* reveals variable number of microorganisms. Positive serology for syphilis is helpful in confirming the diagnosis.

Differential Diagnosis

The differential diagnoses of benign lymphoid hyperplasia secondary to syphilis are broad given the potential of syphilis to mimic virtually any entity and include lymphoma, reticulohistiocytoma, Hodgkin's disease, lymphomatoid papulosis, and diffuse Kaposi sarcoma (Rashidi et al. 2012) since all of these entities are characterized clinically by a papulosquamous/papulonodular eruption and histopathologically by a dense dermal lymphoplasmacytic infiltrate (Shiino et al. 2012).

Herpes

Definition

Worldwide rates of herpes simplex virus (HSV) infection (herpesviruses; HSV type 1 and HSV type 2) are between 65 and 90 % (Chayavichitsilp et al. 2009). In the United States, the prevalence of HSV-1 was 57.7 % as per a 1999–2004 study (Xu et al. 2006). The data for HSV-2 published in March 2010, based on a National Health and Nutrition Examination Survey study performed between 2005 and 2008 by Centers for Disease Control and Prevention (CDC), revealed about one in six Americans (16.2 %) aged 14–49 is infected with HSV-2. HSV-2 prevalence was nearly twice as high among women (20.9 %)

than men (11.5 %) and was more than three times higher among blacks (39.2 %) than whites (12.3 %) (Xu et al. 2010). HSV-1 especially recurrent disease usually occurs around the lips (herpes labialis). Infection with HSV-2 generally involves the genitalia and surrounding areas and usually sexually transmitted. The usual lesions of herpes simplex consist of a group of clear vesicles. Herpes varicella/zoster virus (VZV) affects 10–20 % of the population with an increased incidence in the elderly and in those who are immunocompromised (Spray and Glaser 2002). An estimated one million cases of herpes zoster occur each year in the United States (Weinberg et al. 1993). It results from reactivation of latent varicella/zoster virus (VZV) infection.

Clinical Features

The characteristic rash has a unilateral dermatomal distribution that most often affects the thoracic and lumbar regions, and sometimes the face although any dermatome can be affected.

Histopathology

The histopathologic appearances of herpes simplex and herpes zoster are very similar and pseudolymphomas caused by both have been reported. Histopathologically, there are epidermal vesicles containing multinucleate ballooning and acantholytic keratinocytes with viral inclusion bodies. In addition there is a dermal inflammatory infiltrate composed of lymphocytes and occasional neutrophils. Atypical large lymphoid cells may be present in the infiltrate. In one study reported by Resnick and Dileonardo, 2010, approximately 70 % of the specimens (32 of 45 cases) showed atypical T lymphocytes. In a study of 65 patients with herpes simplex (HSV-1 and/or 2) and herpes varicella/zoster (VZV), histopathology examination revealed features simulating malignant lymphoma. Briefly these included a dense lymphoid infiltrate, angiotropism, and atypical T lymphocytes (Leinweber et al. 2004). A rapid cytological diagnosis of a vesicular lesion can be made by making a smear from the base of a freshly opened vesicle and staining it with the Giemsa stain (Tzanck test).

Immunophenotype, Cytogenetics, and Molecular Findings

Immunoperoxidase stains and PCR studies with probes specific for HSV-1, HSV-2, and VZV are now available commercially. Immunohistochemistry performed in cases with dense atypical lymphocytes showed a strong preponderance of T lymphocytes with admixed B lymphocytes and scattered CD30+ and CD56+ cells, supporting the T lymphocytes' nature of herpes-induced pseudolymphomas (Leinweber et al. 2004). Heavy-chain gene rearrangement is typically not seen and there is usually no light-chain restriction of plasma cells. Of note, two cases with morphologically pseudolymphomatous appearance histopathologically were found to have a monoclonal population of T lymphocytes by PCR analysis (Leinweber et al. 2004). However, the diagnosis of CPL was confirmed by the presence of histopathology evidence of viral inclusions and PCR analyses.

Differential Diagnosis

The differential diagnosis includes CBCL and CTCL. Helpful differentiating features are the same as those mentioned before under the section of differential diagnosis in an idiopathic lymphocytoma cutis.

Pseudolymphoma at Sites of Vaccination

Definition

This is a relatively rare reaction pattern characterized by a florid lymphocytic inflammatory reaction either immediately or as a delayed hypersensitivity reaction to a vaccine constituent, including aluminum and thimerosal (Chong et al. 2006). There are no precise data concerning the incidence, prevalence, and geographic distribution of this reaction although given the number of reports of this entity in the literature (<15 between 1993 and 2012), it appears to be uncommon. Vaccines associated with this reaction pattern include those to varicella zoster, hepatitis B, early

summer meningoencephalitis (Facchetti et al.), tetanus, diphtheria, pertussis, and measles, mumps, and rubella (MMR).

Clinical Features

The clinical presentation is usually that of superficial papules or nodules, at the vaccination site (Cerroni et al. 2007). These may arise immediately or from weeks to months to even, albeit rarely, years after the vaccination.

Histopathology

Histopathologically, about 20 % of the persistent nodules at the vaccination sites showed lymphoid follicles with reactive germinal centers (Fig. 7.7a–c) and a prominent perifollicular infiltrate. Other observed reaction patterns include a lichenoid dermatitis, panniculitis (septal or mixed), and "granuloma annulare-like" (with a palisaded histiocytic infiltrate surrounding foci of necrobiosis) (Chong et al. 2006).

Immunophenotype, Cytogenetics, and Molecular Findings

The demonstration of aluminum by Morin staining and atomic absorption spectrometry on a paraffin-embedded tissue probe can be used to support the diagnosis of vaccination-induced pseudolymphoma. Immunohistochemical analysis reveals a mixed-cell infiltrate containing both CD3-positive T lymphocytes and CD20-positive B lymphocytes. The plasma cells typically show polyclonal expression of immunoglobulin light chains kappa and lambda, and there is no heavy-chain gene rearrangement.

Clinical Course

Lesions may persist for months or years despite intralesional steroid therapy.

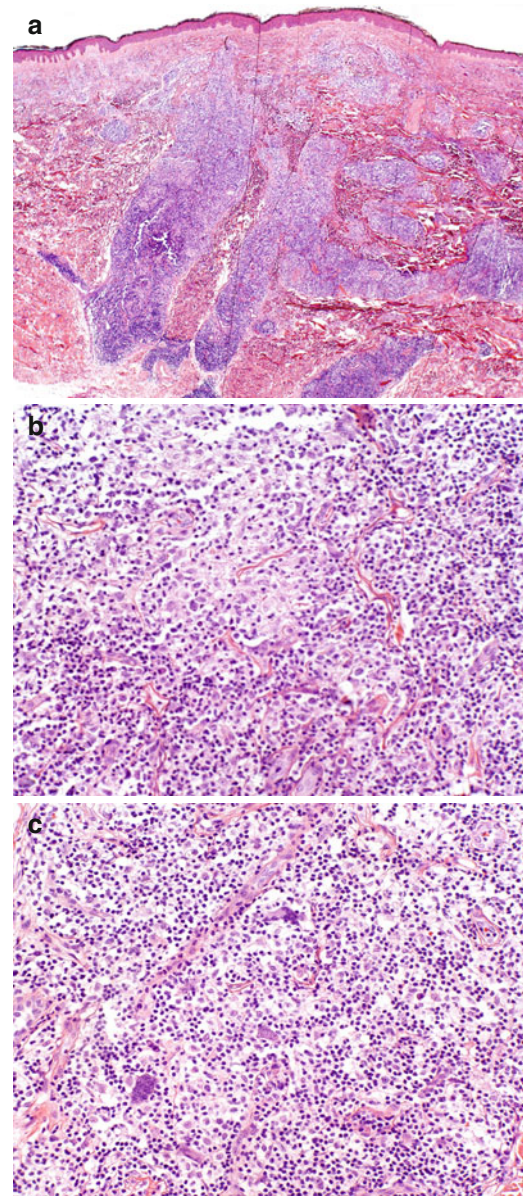

Fig. 7.7 (**a**–**c**) Reactive cutaneous B-cell nodular lymphoid hyperplasia at hepatitis B vaccine site (H&E). (**a**) Scanning magnification revealing inflammation adjacent scar tract, (**b**) nodular lymphocytic infiltrate with germinal center formation, (**c**) admixed multinucleate giant cells

Differential Diagnosis

The differential diagnosis includes CBCL and CTCL (depending on whether the infiltrate is B or T lymphocyte rich). Helpful differentiating

features from CBCL are the same as those mentioned before under the section of differential diagnosis in idiopathic lymphocytoma cutis.

Persistent Nodular Arthropod-Bite Reaction and Nodular Scabies

Definition

This reaction pattern develops most commonly as a result of infestation with the itch mite, Sarcoptes scabiei var. hominis) although it has been known to occur secondary to other arthropod bites. While the cause is not precisely known, it is believed to be a manifestation of a delayed-type hypersensitivity reaction to a component of the mite (Ploysangam et al. 1998).

Scabies is a worldwide disease and a major public health problem in many developing countries, related primarily to poverty and overcrowding. In remote communities in northern Australia, prevalence of up to 50 % among children has been described, despite the availability of effective therapy (Walton and Currie 2007). There are about 300 million cases of scabies in the world each year (Hicks and Elston 2009). An infested person can very easily pass scabies to his or her household members and sexual partners. Scabies in adults frequently is sexually acquired. In the United States and in other developed regions around the world, scabies occurs in epidemics in the institutions such as nursing homes, extended-care facilities, childcare facilities and prisons, and homeless population.

Clinical Features

The clinical presentation is that of multiple, extremely pruritic, firm, round to oval, erythematous to red-brown papules and nodules occurring most commonly between the fingers, wrist, elbows, abdomen, genitalia, nipple, buttocks, shoulder blades, and axillae (Ploysangam et al. 1998). When a person is infested with the scabies mite for the first time, lesions may be asymptomatic for the first 2 months, although an infested person still can spread scabies during this asymptomatic time. If a person has had scabies previously, symptoms appear much sooner (1–4 days) after exposure.

Histopathology

Histopathologically, this reaction pattern is characterized by a dense, superficial and deep, predominantly perivascular lymphohistiocytic infiltrate with eosinophils (Fig. 7.8a–c). Of note, the scabetic mite is seldom identified in a scabetic nodule. Prominent thickened wall vessels lined by reactive endothelial cells and epidermal change (hyperkeratosis and epidermal hyperplasia with mild spongiosis) are frequently seen (Fernandez et al. 1977). Vasculitis can be found in those cases showing tissue eosinophils, an exuberant inflammatory tissue reaction, and many mites. Both the number of circulating eosinophilic granulocytes and serum IgE concentrations correlate with the severity of the skin reaction. In one study, ten of 60 patients (17 %) with scabies had markedly increased numbers of circulating eosinophils during scabies infestation. In most of the patients, however, the number of circulating eosinophils decreased after treatment (Falk and Eide 1981).

Immunophenotype

Immunohistochemical stains indicate a mixed-cell infiltrate containing both T (CD3-positive) and B (CD20-positive) lymphocytes – features arguing in favor of a benign reactive pattern. CD30 may highlight scattered large lymphocytes.

Cytogenetics and Molecular Findings

There is no heavy-chain gene rearrangement and a polyclonal reaction pattern is seen in the immunoglobulin light chains.

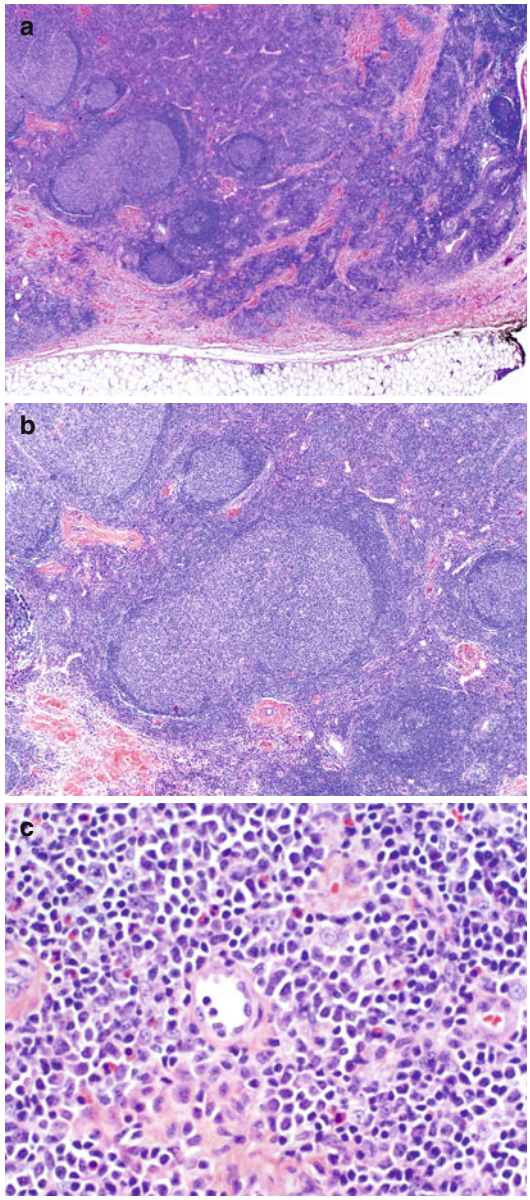

Fig. 7.8 (**a**–**c**) Reactive nodular lymphoid hyperplasia secondary to an arthropod bite (H&E). (**a**) scanning magnification revealing deep, nodular lymphoid infiltrate, (**b**) reactive follicles, (**c**) admixed eosinophils

Clinical Course

Nodules following infestation with Sarcoptes scabiei var. hominis may persist for many months after adequate anti-scabetic therapy. Spontaneous resolution is seen in all persistent arthropod-bite reactions.

Differential Diagnosis

The differential diagnoses include prurigo nodularis, pseudolymphoma, and lymphoma (CBCL and CTCL). Presence of the scabetic mite, eosinophils, and increased circulating eosinophils and serum IgE are useful clue to the diagnosis. To differentiate from malignant lymphoma, helpful features are as the same as those mentioned earlier (idiopathic lymphocytoma cutis section).

Conclusion

There is no single histopathology criterion to differentiate CBPL from CBCL. Histologic diagnosis of CBPL depends on two considerations: (1) the architecture of the infiltrate and (2) the composition and cytomorphology of cells in the infiltrate. Histopathologic features that favor CBPL over CBCL include (1) acanthosis, (2) a top-heavy infiltrate, (3) a mixed (T- and B-lymphocyte-rich) infiltrate, (4) absence of mitosis outside of the germinal center and/or necrosis, (5) regular appearing germinal centers, (6) presence of tingible bodies in the germinal centers, (7) lack of cohesion of lymphoid cells, (8) infiltrative border (concave), (9) preservation of adnexal structures with the infiltrate respecting adnexal epithelium, and (10) stromal fibrosis (Ploysangam et al. 1998). A useful immunohistochemical feature for distinguishing cutaneous follicle-center cell lymphoma from cutaneous lymphoid hyperplasia is the presence of small clusters of CD10+/Bcl6+ lymphocytes in the interfollicular zones and positive Bcl2 staining in the follicles in the former. Furthermore, there is a low MIB-1 proliferation fraction in lymphoma compared with cutaneous lymphoid hyperplasia.

Mimics

Inflammatory Pseudotumor

Definition

Inflammatory pseudotumor (IPT) also known as inflammatory myofibroblastic tumor (IMT) or plasma cell granuloma (PCG) is a distinct,

heterogeneous group of mesenchymal tumors composed of various proportions of myofibroblasts, hyalinized collagenous stroma, and admixed inflammatory cells. It is known to occur in any part of the body and has varied morphology. The one most relevant to this chapter is cutaneous inflammatory myofibroblastic tumor (IMT) or plasma cell granuloma (PCG) – a spectrum of idiopathic benign conditions with pseudolymphomatous pattern, a mixed-cell infiltrate containing numerous plasma cells, prominent germinal centers, and a proliferation of myofibroblasts (Coffin et al. 2007).

Clinical Features

Cutaneous IMT usually presents as a solitary, slowly growing, tender, firm cutaneous, or subcutaneous papule or nodule measuring 1–5 cm in diameter (El Shabrawi-Caelen et al. 2004).

Histopathology

Histopathologically, there is a heavy inflammatory cell infiltrate containing numerous plasma cells with prominent reactive germinal centers dispersed throughout the lesion mimicking CPL or lymphoma (Coffin et al. 1998). Other features include the presence of high endothelial venules, admixed eosinophils and histiocytes, calcification, and large atypical myofibroblasts (CD15–, CD30–, vimentin +) simulating Reed-Sternberg cells (Carlson et al. 2001; El Shabrawi-Caelen et al. 2004; Hurt and Santa Cruz 1990; MacSweeney and Desai 2000; Ramachandra et al. 1995; Yang 1993).

Immunophenotype

CD3 marks small, reactive T lymphocytes, and CD20 detects focal clusters of reactive B lymphocytes (El Shabrawi-Caelen et al. 2004).

Cytogenetics and Molecular Findings

Plasma cells showed a polyclonal reaction pattern with kappa and lambda immunoglobulin light chains. Immunoglobulin heavy-chain gene reveals a polyclonal pattern.

Differential Diagnosis

Main differentiating features from lymphoma especially Hodgkin's lymphoma are the presence of myofibroblasts (CD15–, CD30–, vimentin +) and the density of plasma cells. Differences in the biological behavior (recur locally) and molecular profile (>50 % of cases reveal ALK gene rearrangement) are also of utility in differentiating this entity from ALK-negative IMT lesions with more aggressive clinical course (Coffin et al. 2007).

Lymphocytic Infiltration of the Skin (of Jessner and Kanof)

Definition

Lymphocytic infiltration of the skin (of Jessner and Kanof) or Jessner's lymphocytic infiltrate, a relatively uncommon condition of unknown etiology, was first introduced by Jessner and Kanof in 1953 (Jessner and Kanof 1953). This entity is now regarded as a variant of tumid LE (Remy-Leroux et al. 2008).

Histopathology

Histopathologically, this entity is characterized by a moderately dense, superficial and deep, perivascular and periappendageal infiltrate with occasional involvement of the subcutis. The infiltrate is composed predominantly of small lymphocytes although larger lymphocytes, mimicking CPL, may be present (Cerio et al. 1990; Facchetti et al. 1990; Helm and Muller 1992; Konttinen et al. 1987; Kuo et al. 1994; Willemze et al. 1984).

Immunophenotype

The infiltrate is predominantly T (CD3+) lymphocyte rich with a smaller component of CD20+ B lymphocytes, and negative staining with CD5 and CD43 helps differentiate this entity from cutaneous lesions of CBCL especially CLL.

Cytogenetics and Molecular Findings

The mixed (T and B lymphocytes) and polyclonal nature of the lymphoid infiltrate in Jessner's lymphocytic infiltrate help differentiate this entity from cutaneous lesions of CBCL.

Clinical Course

Lesions often resolve within weeks or months, but recurrences/relapses may occur in the same

or different area. The average duration of the disease is 5 years (Toonstra et al. 1989).

Differential Diagnosis

In contrast to CBPL, mucin may be seen between collagen bundles. It has mostly benign, but unpredictable clinical behavior.

Granulomatous Rosacea

Clinical Features

Granulomatous rosacea usually presents as noninflammatory, hard, brown, yellow or red, uniformly sized cutaneous papules or nodules on the cheeks, and periorificial facial skin, although extrafacial lesions have been reported in a minority (15 %) of patients (Helm et al. 1991; Wilkin et al. 2002).

Histopathology

Histopathologically, in granulomatous rosacea, a multinodular, granulomatous, perifollicular, and perivascular lymphohistiocytic infiltrate with varying numbers of multinucleate giant cells is usually seen in the superficial and/or mid-dermis. The infiltrate may be primarily lymphocytic in up to 40 % of patients and primarily histiocytic in up to 34 % of patients. Other features include the presence of damaged follicles, and/or the mite D. folliculorum and marked vascular dilatation (Amichai et al. 1992). The perifollicular granulomas may be noncaseating (epithelioid granulomas in 11 % of patients) or caseating (epithelioid granulomas with caseating necrosis in 11 %) reaction (Helm et al. 1991).

Immunophenotype

Small, reactive T lymphocytes are highlighted by CD3, and CD20 detects focal clusters of reactive B lymphocytes.

Cytogenetics and Molecular Findings

A polyclonal pattern of the immunoglobulin heavy-chain gene is detected by PCR study. No immunoglobulin light-chain restriction is seen.

Differential Diagnosis

Differentiating features from CBPL are the presence of perifollicular lymphocytes and histiocytes with admixed multinucleate giant cells, damage follicles and/or mite D. folliculorum, marked vascular dilatation and the presence of lesion clinically confined to the head and neck area.

Clonality: Significance

In cases with a discrepancy between the clinical, histologic, and immunohistochemical studies, a search for gene rearrangements in both T and B lymphocytes is useful. Generally, benign or reactive processes are polyclonal, whereas the presence of monoclonality directs a malignant process. However, this distinction is not absolute because numerous studies have shown that cutaneous lymphoid hyperplasia, diagnosed both clinically and histologically, harbors a clonal B-lymphocyte population in 4–62 % of cases, as evidenced by monotypic plasma cells or immunoglobulin gene rearrangement (Bergman et al. 2011; Boer et al. 2008; Ceballos et al. 2002; Wechsler et al. 1990; Weinberg et al. 1993). Therefore, the interpretation of clonality result must be done in the context of the clinicopathologic and immunohistochemical features of cutaneous lymphoproliferative processes. Cases of CPL cases with a positive clone should be followed up carefully because a small minority may develop into overt lymphoma (Bergman et al. 2011). Also see differential diagnosis section in cutaneous lymphoid hyperplasia secondary to foreign body's reaction to tattoo.

Clues to Diagnosis: Clinical and Histopathologic

Clinical manifestations of cutaneous pseudolymphoma are variable and usually not helpful for differentiating a benign from a malignant lymphoid process. While benign lesions present most commonly as a solitary nodule, multiple lesions have been reported, albeit rarely. Benign lesions can also present as erythroderma. Benign lesions clinically have a doughy to firm consistency and range from red brown to violaceous in color. Lesions may be pruritic or asymptomatic (Boudova et al. 2005).

Table 7.1 Cutaneous B-cell pseudolymphoma (CBPL) versus cutaneous B-cell lymphoma (CBCL) – helpful differentiating features

	CBPL	CBCL
Clinical features		
Number of lesions	Solitary or multiple	Usually solitary
Extracutaneous involvement	Absent	Possible
Recurrences	Rare	Likely
Histopathologic features		
Acanthosis	Prominent	Minimal or no
Pattern of infiltrate	Nodular (>90 %)	Diffuse or nodular
Structure of infiltrate	Top heavy (75 %)	Bottom heavy (65 %)
Border of the infiltrate	Concave, poorly demarcated	Convex, sharply demarcated
Additional cells (e.g., eosinophils, plasma cells) and epithelioid cell granulomas	Usually present	Less common
Germinal center	More preserved (65 %)	Less preserved (10–20 %)
Mantle zone	Present	Usually absent
Polarity of GC cells	Retained	Loss
Effaced lymphoid follicles	Usually absent	Present
Tingible body macrophages (fragmented basophilic nuclear debris of degenerated lymphoid cells)	Present	Usually absent
Mixed-cell infiltrate with small lymphocytes	Present predominantly in the upper dermis	Less common
Sparing of epithelial and adnexal structures	Present	Usually absent
Immunophenotype		
Immunoglobulin light chain	Polytypic expression (kappa or lambda)	Monotypic expression
B -cell marker expressing cells	<50 % cells (predominantly within the follicles)	>50 % cells
T-cell marker expressing cells	>50 % cells (predominantly outside and between the follicles)	Usually few
CD21-positive dendritic cells	Regular pattern (evenly distributed)	Irregular pattern
MIB-1 immunostain (proliferative rate)	High	Low
Germinal center		
CD10 and Bcl6	Positive	Negative
Bcl2	Negative	Positive
Genotype		
Ig heavy-chain gene rearrangement	Absent in most cases	Present in most cases

Histopathologic clues to the diagnosis of a reactive lymphoid hyperplasia versus one that is malignant include the presence in the former of a mantle zone, polarity of GC cells, absence of effaced lymphoid follicles, tingible body macrophages, mixed-cell infiltrate with small lymphocytes mainly involving the upper dermis, sparing of epithelial and adnexal structures, CD20-positive B lymphocytes predominantly within the follicles, CD3-positive T lymphocytes predominantly outside and between the follicles, evenly distributed CD21 follicular dendritic cells, high proliferative rate as evidence by MIB-1 immunostain, GC cells with positive staining for CD10 and Bcl6, but negative/rare positive staining for Bcl2, the presence of eosinophils, and absence of clonality (Table 7.1). None of the aforementioned criteria, however, is discriminative by itself, and the diagnosis is based on a constellation of several findings (Caro and Helwig 1969).

Acknowledgments The authors would like to acknowledge Amy C Mueller, BA for assistance with formatting and cataloguing of references.

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