3 Role of Immunohistochemistry and Chromogenic In Situ Hybridization in Diagnosis

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Introduction

Immunohistochemistry utilizes antigen-antibody recognition in detecting specific antigens within tissues. Due to technical advances, there has been a significant increase in the number of diagnostic immunohistochemical stains and chromogenic in situ hybridization available to pathologists in recent years. The sensitivity and specificity of each antibody, its pattern of staining (nuclear, cytoplasmic, or membranous), and background artifact must be considered in its interpretation. In addition, evaluation must be done in relation to internal controls. In the diagnosis of lymphoid infiltrates, a panel of immunohistochemical markers is helpful in narrowing the differential diagnoses. In this chapter, an update of recently available immunohistochemical stains as well as selected diagnostic panels are outlined. These panels are used to distinguish reactive lymphoid hyperplasia from low-grade B-cell lymphoma, diffuse cutaneous follicle center cell lymphoma from diffuse large B-cell lymphoma, subcutaneous panniculitic T-cell lymphoma from cutaneous gamma-delta T-cell lymphoma, CD30-positive lymphoproliferative disorders from reactive processes, follicular mucinosis from folliculotropic mycosis fungoides, and lymphomatoid drug eruption from plaque-stage mycosis fungoides.

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Recently Available Immunohistochemical Markers

PD1

Programmed cell death protein 1 (PD1) is a protein encoded by the *PDCD1* gene (Shinohara et al. 1995) and is a member of T-cell regulators (Ishida et al. 1992). PD-1, a marker of germinal center-associated T cells (Fig. 3.1a), is expressed by neoplastic cells in primary cutaneous CD4+ small-/medium-sized pleomorphic T-cell lymphoma (Rodriguez Pinilla et al. 2009) and angioimmunoblastic T-cell lymphoma (Dorfman et al. 2006). Its expression can be seen in cutaneous pseudo-T-cell lymphoma; thus, PD-1 is *not* a helpful diagnostic marker in the distinction of a reactive T-cell process from cutaneous CD4+ small-/medium-sized pleomorphic T-cell lymphoma (Cetinozman et al. 2012).

CD123

CD123, interleukin-3 receptor alpha (Munoz et al. 2001), is a marker of plasmacytoid dendritic cells and the blastic plasmacytoid dendritic cell neoplasm. A tumor characterized by dense

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monomorphous infiltrates of medium-sized blastoid cells positive for CD4, CD56, and CD123 (Cota et al. 2010; Facchetti et al. 2008).

CD14

CD14 has been reported to be a specific marker for monocytic differentiation, but with low sensitivity in comparison to CD68 (Klco et al. 2011).

B-Cell Transcription Factors Including MUM1/IRF-4, PAX5, OCT2, and BOB.1

The multiple myeloma oncogene 1 (*MUM1*)/interferon regulator factor 4 (*IRF4*) gene encodes the MUM1 protein which is normally expressed in plasma cells, a small fraction of B cells, and activated T cells (Gualco et al. 2010). MUM1 expression is seen in several malignancies including plasma cell myeloma (Iida et al. 1997),

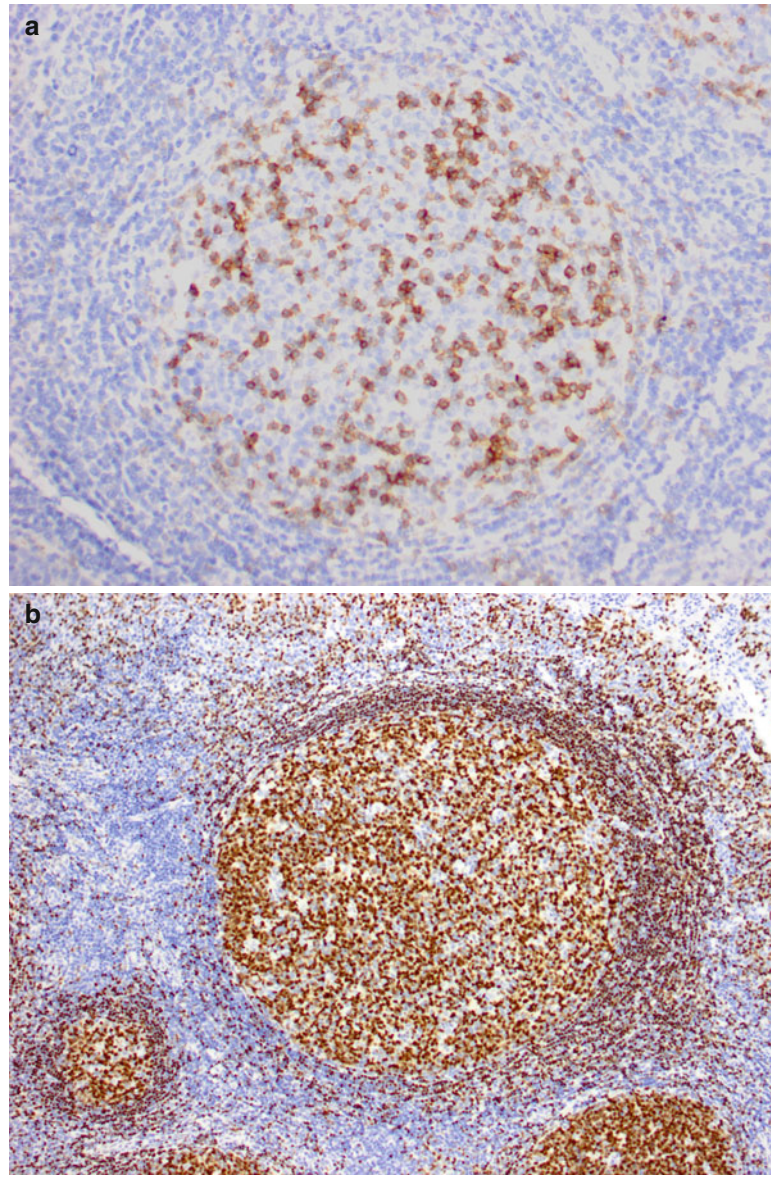
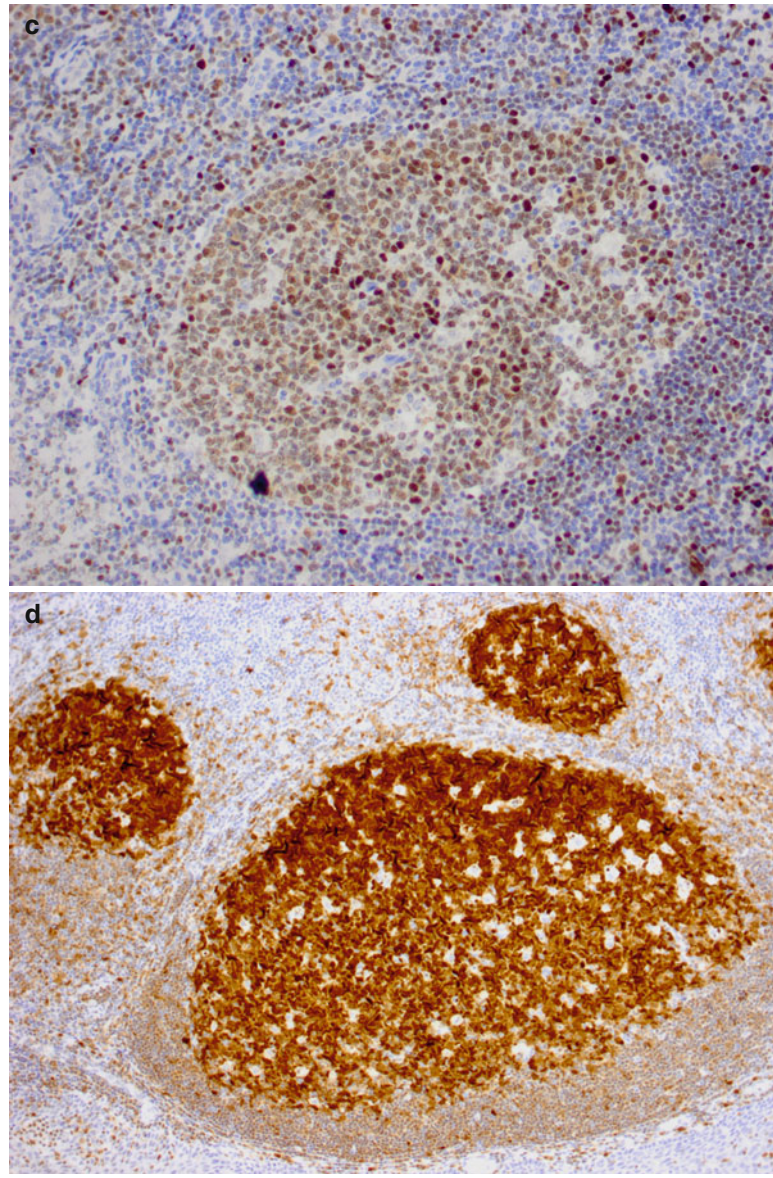


Fig. 3.1 PD1 (**a**), PAX5 (**b**), OCT2 (**c**), and BOB.1 (**d**) immunostaining of a reactive germinal center

Fig. 3.1 (continued)



diffuse large B-cell lymphomas (especially cutaneous diffuse large B-cell lymphomas, leg type), and systemic anaplastic large cell lymphomas (Tsuboi et al. 2000; Natkunam et al. 2001; Hoefnagel et al. 2003).

PAX5 (paired box gene 5) is a pan B- and pan pre-B-cell marker present in most B-cell neoplasms (both mature and immature) (Fig. 3.1b). Approximately one-third of plasma cell neoplasms express PAX5. Reed-Sternberg cells of classical Hodgkin lymphoma and the L&H (lymphocyte and histiocytic) cells of nodular lymphocyte predominant Hodgkin lymphoma are PAX5 positive (Torlakovic et al. 2002). PAX5 is also expressed in some anaplastic large cell lymphomas (Feldman et al. 2010).

OCT2 is a transcription factor restricted to B lymphocytes and is associated with BOB.1, a

B-cell transcriptional coactivator (Krenacs et al. 1998) (Fig. 3.1c). BOB.1 is less lineage specific than OCT2, being expressed in T-cell as well as B-cell lymphomas (Fig. 3.1d). BOB.1 is strongly positive in a range of non-Hodgkin lymphomas. It is generally not expressed in classical Hodgkin lymphoma; however, weak expression has been reported, making interpretation challenging.

TCR Gamma

The T-cell receptor (TCR) is comprised of two ligand-binding glycoproteins containing variable regions (alpha-beta and gamma-delta) (Rojo et al. 2008). The gamma-delta T cells can comprise up to 16 % of T cells in mucosal sites, particularly the intestine and skin (Groh et al. 1989). Rodriguez-Pinilla et al. (2013) found the expression of TCR gamma to be a characteristic feature of primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL) (5/5), although its expression was also noted in other primary cutaneous lymphomas including isolated cases of mycosis fungoides (MF) and lymphomatoid papulosis (LyP) type D, representing approximately 8 % of the 146 primary cutaneous T-cell lymphoma (CTCL) cases analyzed. While TCR beta F1 antibody has been available for decades, TCR-gamma-delta antibody has become available only recently (Krajewski et al. 1989; Rodriguez-Pinilla et al. 2013).

Reactive Lymphoid Hyperplasia Versus Low-Grade B-Cell Lymphoma

The differential diagnosis of cytologically low-grade lymphoid proliferations in the skin includes reactive lymphoid hyperplasia, primary cutaneous marginal zone B-cell lymphoma (PCMZL), and primary cutaneous follicle center lymphoma (PCFCL). Nonneoplastic or reactive lymphoid proliferations mimicking lymphoma ("pseudolymphoma") typically consist of a mixed population of B and T lymphocytes (Cerroni et al. 2000). Variable quantities of scattered CD3 and CD20 staining can help to establish the reactive nature of the lymphoid infiltrate. The germinal center cells of reactive lymphoid follicles are CD20+, CD79a+, Bcl2−, and Bcl6+, while cells of the mantle zone are Bcl2+ (Hoefnagel et al. 2003). Reactive germinal center cells as well as scattered interfollicular cells may stain for CD10 (Hoefnagel et al. 2003; Cerroni et al. 2000). For reactive populations, evaluation of B lymphocytes by light chain in situ hybridization should demonstrate a mixed kappa and lambda population (Levy et al. 1977). Reactive follicles also tend to show Ki-67 staining in the vast majority of germinal center cells, whereas the cells in the neoplastic follicles of PCFCL frequently show less than 50 % positive Ki-67 staining (Cerroni et al. 2000).

PCMZL is characterized by peri- and interfollicular proliferation of marginal zone cells (small- to medium-sized cells with indented nuclei and pale cytoplasm) which are CD20+, CD79a+, Bcl2+, Bcl6−, CD5−, and CD10− (Servitje et al. 2002; de Leval et al. 2001; Cerroni et al. 2000) (Fig. 3.2). In contrast to cells of PCFCLs, cells of PCMZL are CD5−, CD10−, and Bcl6− (Hoefnagel et al. 2003). Commonly, aggregates of plasma cells are seen at the periphery of the tumor which exhibit kappa or lambda light chain restriction (de Leval et al. 2001; Servitje et al. 2002) (Fig. 3.2). The presence of Bcl2+, Bcl6−, and CD10− infiltrating lymphocytes strongly supports the diagnosis of PCMZL over PCFCL or reactive lymphoid hyperplasia (Hoefnagel et al. 2003); however, reactive interfollicular T cells may also show this staining pattern. PCMZL is often associated with reactive follicles with the CD10+, Bcl2−, and Bcl6+ immunophenotype which may represent a diagnostic pitfall if not recognized (de Leval et al. 2001; Hoefnagel et al. 2003). CD21, a marker of follicular dendritic cells (FDC), often highlights an expanded follicular dendritic meshwork due to colonized neoplastic marginal zone or plasmacytoid cells admixed with reactive follicular cells (de Leval et al. 2001). This pattern of CD21 staining, highlighting the colonized germinal centers with distorted architecture, can be helpful in establishing the diagnosis of PCMZL (Fig. 3.2).

PCFCL characteristically appears as a nodular to diffuse lymphoid proliferation with neoplastic follicle center B cells (centrocytes and centroblasts) which are CD20+, CD79a+, Bcl2−, and Bcl6+ (Cerroni et al. 2000; Hoefnagel et al. 2003). Different authors describe the neoplastic cells as CD10+ (Cerroni et al. 2000), CD10− (Hoefnagel et al. 2003), or CD10 variable (de Leval et al. 2001). CD10-negative PCFCL is often seen in diffuse form or areas of PCFCL. Besides Bcl6 and CD10 as germinal center signature differentiation markers, PAX5 and interferon regulatory factor (IRF) 8 are also useful. While the neoplastic cells of PCFCL are typically Bcl2− (Hoefnagel et al. 2003; Hoefnagel et al. 2005; Cerroni et al. 2000; Child et al. 2001) in contrast to the Bcl2 positivity demonstrated by nodal follicular lymphoma, some authors

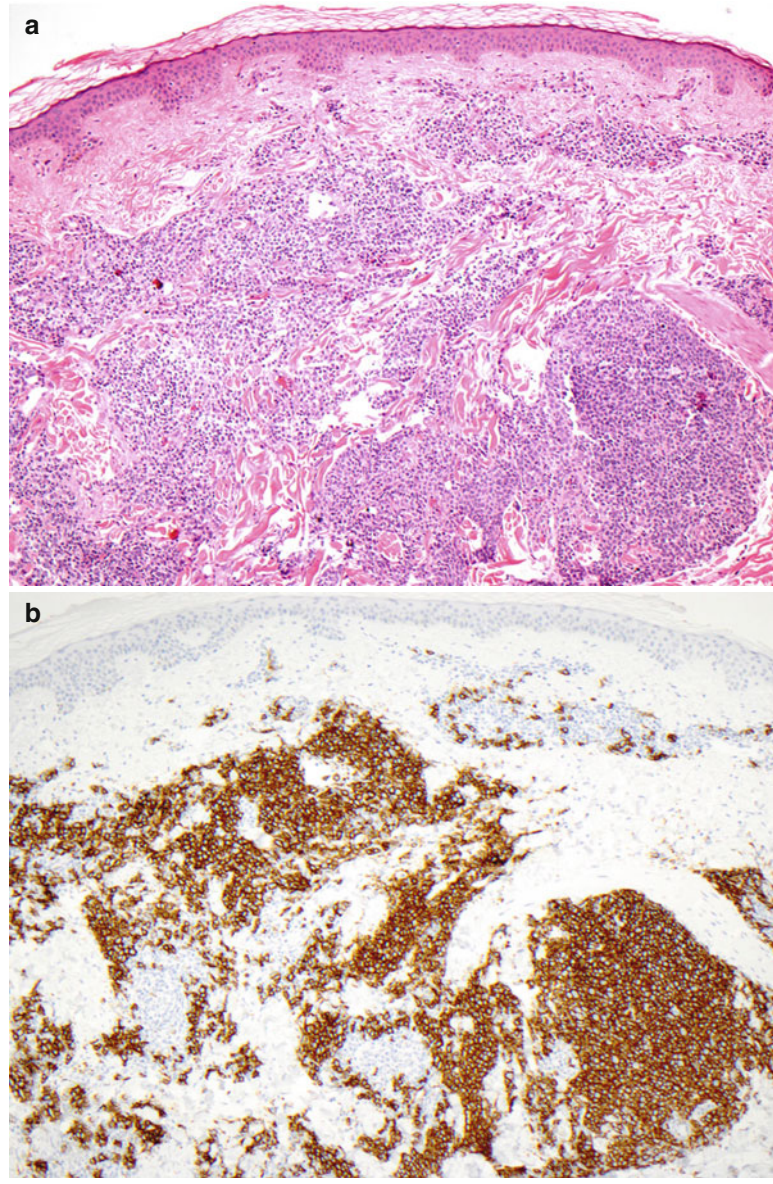


Fig. 3.2 The neoplastic cells of a marginal zone lymphoma (**a**) are positive for CD20 (**b**) and Bcl-2 (**c**). CD21 highlights the expanded follicular dendritic meshwork due to colonized neoplastic cells (**d**). Lambda (**e**) and kappa (**f**) in situ hybridization demonstrate lambda light chain restriction

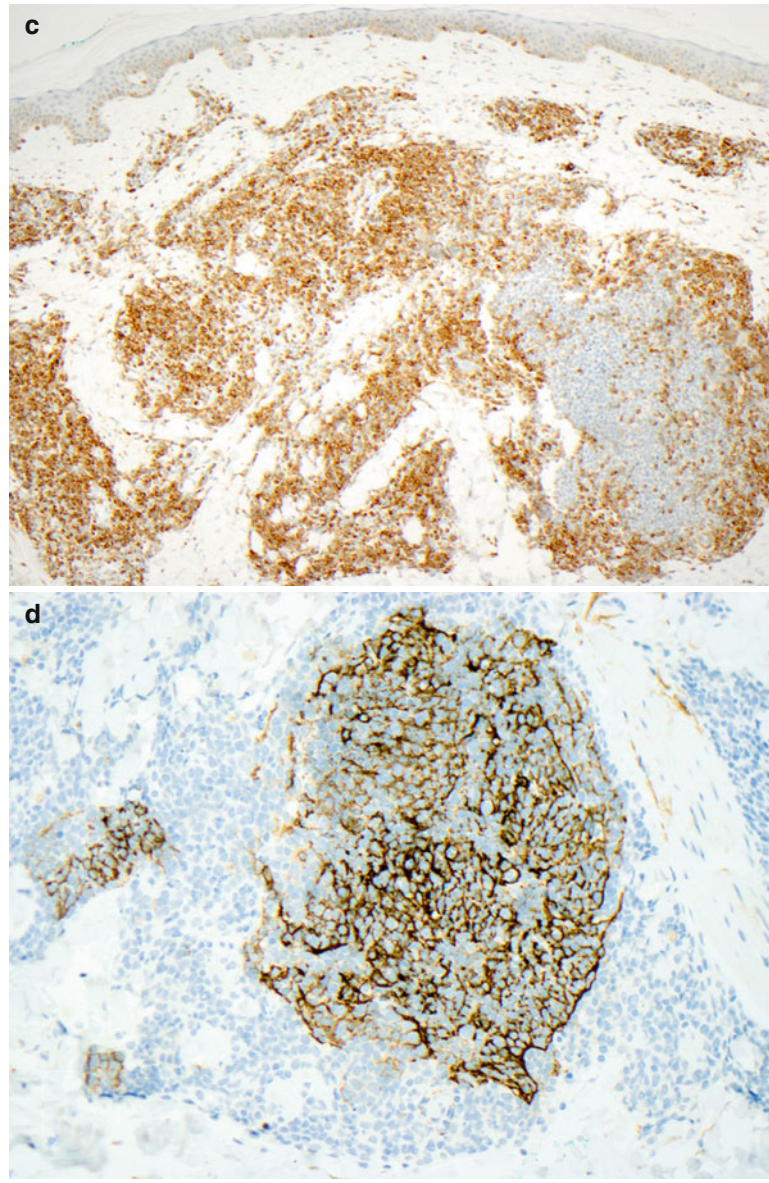
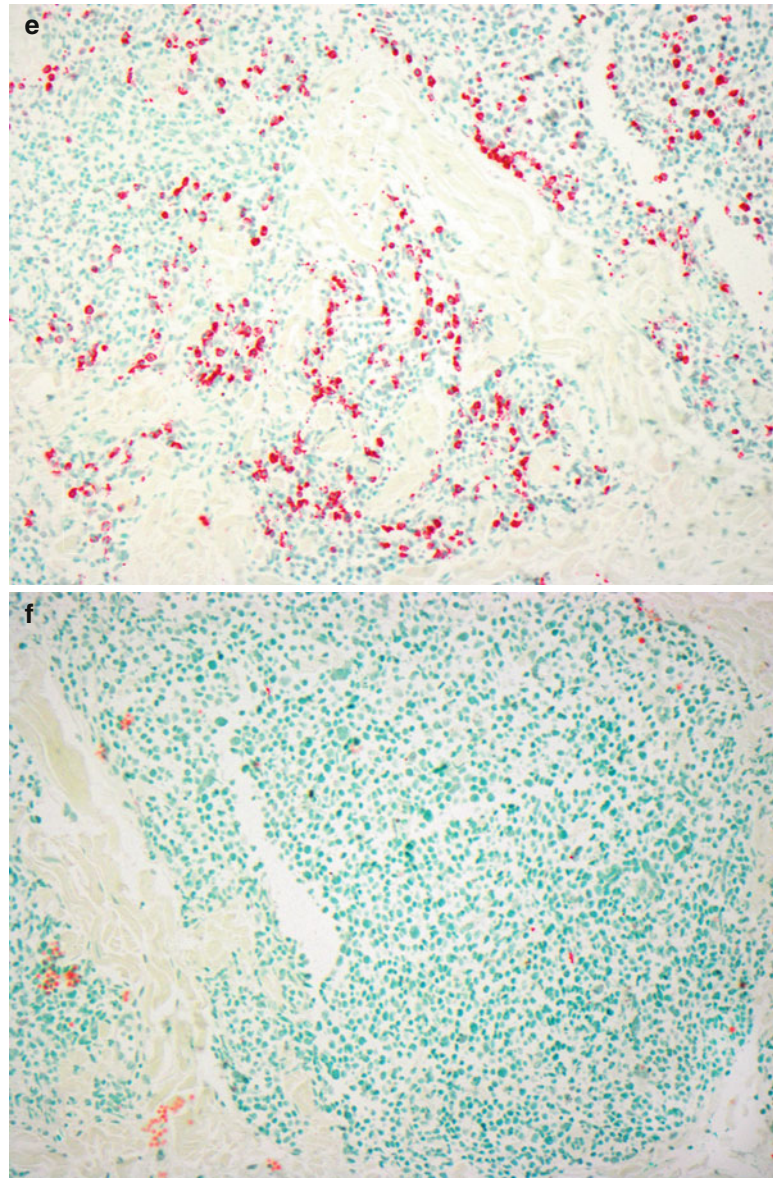


Fig. 3.2 (continued)

have demonstrated cases of PCFCL to be Bcl2+ (de Leval et al. 2001; Goodlad et al. 2002). Moreover, secondary cutaneous involvement of nodal follicular lymphoma is usually Bcl2+, and clinical investigations of BCL2+ cutaneous follicular lymphomas often disclose extracutaneous primary disease. As mentioned above, neoplastic follicles of PCFCL often show less than 50 % positivity for Ki-67 versus reactive follicle cells which are predominately

Fig. 3.2 (continued)



Ki-67 positive (Cerroni et al. 2000). In PCFCL with a prominent nodular arrangement, CD21+ FDCs are present as a sharply defined, thick rim surrounding neoplastic follicles (de Leval et al. 2001; Cerroni et al. 2000).

Recommended panel (Table 3.1): CD3, CD20, Bcl2, Bcl6, CD21, and kappa and lambda in situ hybridization (CD5, CD10, cyclin D1, Ki67, kappa/lambda IHC as additional informative second-line markers)

Table 3.1 Immunoprofile of reactive lymphoid hyperplasia versus low-grade B-cell lymphoma (de Leval et al. 2001; Goodlad et al. 2002)

	Reactive lymphoid hyperplasia	Marginal zone B-cell lymphoma	Follicle center cell lymphoma
CD20	Germinal center +	+	+
Bcl2	Mantle zone + Germinal center –	+	Usually – (+10–25 %)
Bcl6	Germinal center +	–	+
CD21	Intact germinal center	Expanded germinal center	Follicles – Perifollicular rim +
Kappa and lambda in situ hybridization	Mixed light chain expression	Light chain restriction	Light chain restriction

Diffuse Follicle Center Lymphoma Versus Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

The differential diagnosis for a cutaneous large cell lymphoma with a diffuse growth pattern and numerous blasts includes primary cutaneous diffuse large B-cell lymphoma (PCLBCL), leg type, and the diffuse histologic phenotype of primary cutaneous follicle center lymphoma (PCFCL). The distinction between these entities provides critical prognostic information as the 5-year disease-specific survival for PCFCL is 95 %, while that of PCLBCL is only 55 % (Willemze 2006).

As described previously in this chapter, the neoplastic cells of PCFCL are typically positive for CD20 and Bcl6, variably positive for CD10, and usually negative for Bcl2, in contrast to nodal follicular lymphoma (Cerroni et al. 2000; Hoefnagel et al. 2003; de Leval et al. 2001) (Fig. 3.3). In contrast, PCLBCL consists of diffuse proliferation of 90 % or more of medium to large centroblasts and immunoblasts which are typically positive for CD20 and Bcl2 (Fig. 3.3), variably positive for Bcl6, and usually negative for CD10 (Willemze 2006). As these basic lymphocytic markers overlap considerably, additional markers may be required to support a specific diagnosis.

IHC for MUM1, IgM, HGAL (human germinal center-associated lymphoma), and FoxP1 have also been studied for the purpose of distinguishing PCFCL and PCLBCL (Table 3.2). In one study, all cases of PCLBCL demonstrated at least 30 % of cells positive for MUM1, while all cases of PCFCL were negative for MUM1, showing 10 % or less positivity (Hoefnagel et al. 2005; Pham-Ledard et al. 2010; Xie et al. 2008). While other studies have also demonstrated the specificity of MUM1 for PCLBCL (Kodama et al. 2005; Senff et al. 2007), one study classified 50 % of PCFCL cases as MUM1+ (Xie et al. 2008). In two separate studies, IgM staining has been shown to be positive in 100 % of PCLBCL cases and negative in all or nearly all cases of PCFCL (Koens et al. 2010; Demirkesen et al. 2011). The germinal center marker HGAL is positive in 88 % of PCFCL and only 33 % of PCLBCL (Xie et al. 2008). In one series, IHC for FoxP1 was shown to stain ≥50 % of cells in all cases of PCLBCL, while the neoplastic cells of PCFCL are either entirely negative or only 5-10 % positive for FoxP1 in nearly all cases (Hoefnagel et al. 2006).

Recommended panel (Table 3.2): CD20, Bcl2, Bcl6, MUM1, and IgM (also FoxP1 and HGAL, if available)

Subcutaneous Panniculitic T-Cell Lymphoma Versus Cutaneous γ/δ T-Cell Lymphoma

The WHO-EORTC classifications of subcutaneous panniculitic T-cell lymphoma (SPTCL) and cutaneous γ/δ T-cell lymphoma (CGD-TCL) often demonstrate overlapping histopathologic features (Willemze et al. 2005, 2008; Salhany

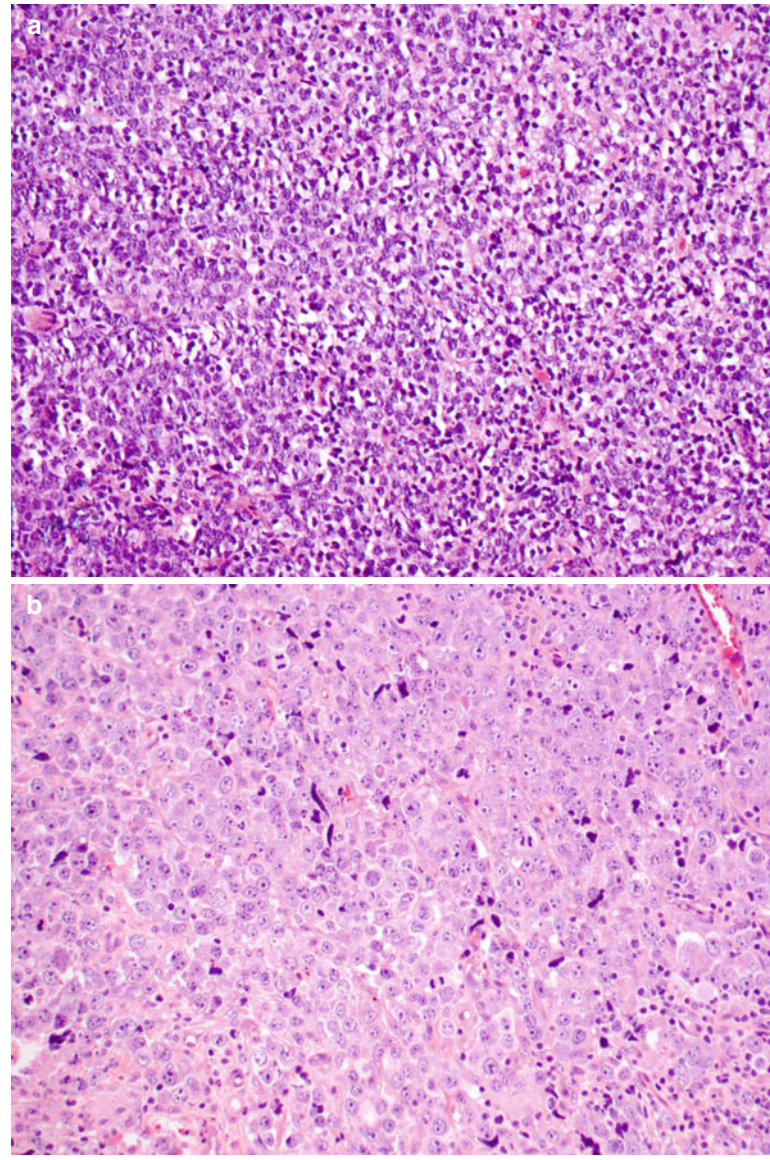


Fig. 3.3 For both diffuse follicle center cell lymphoma (**a**) and diffuse large B-cell lymphoma, leg type (**b**), strong CD20 (**c**, **d**) expression is seen for both. While Bcl2 (**e**) and MUM1 (**g**) expression is focal in diffuse follicle center cell lymphoma, diffuse and strong Bcl2 (**f**) and MUM1 (**h**) expression is seen diffuse large B-cell lymphoma, leg type

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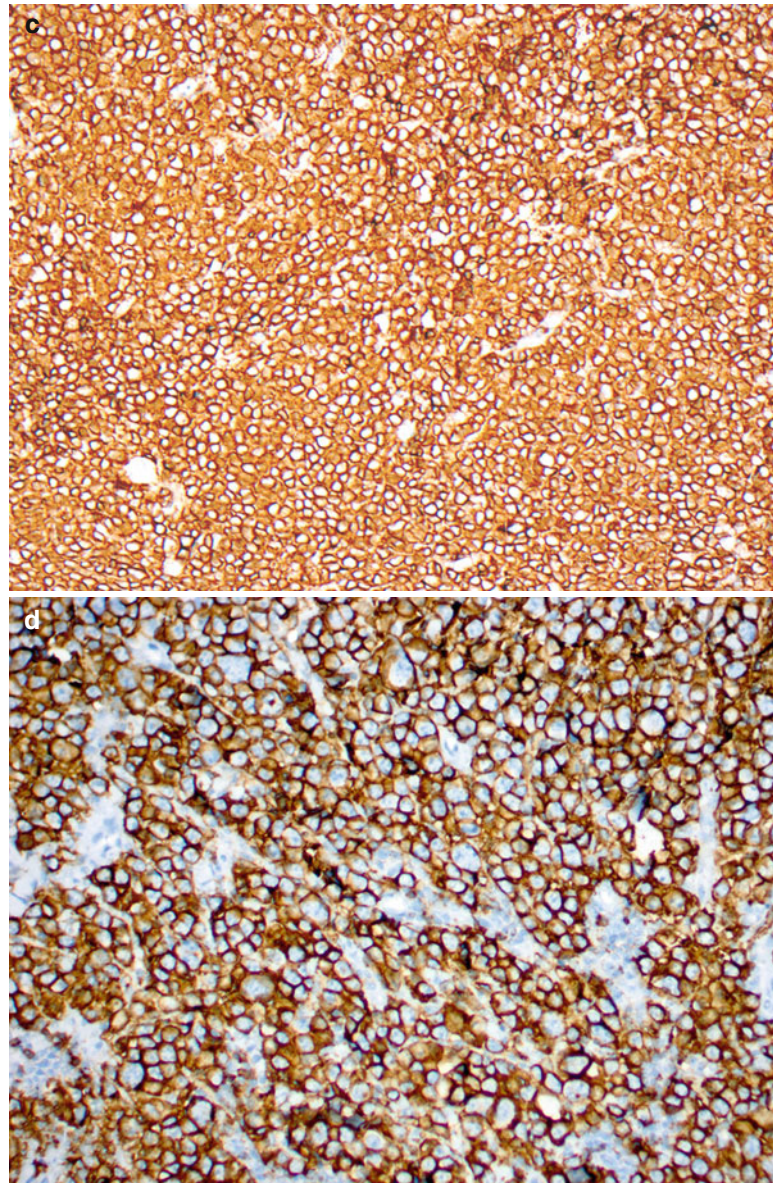

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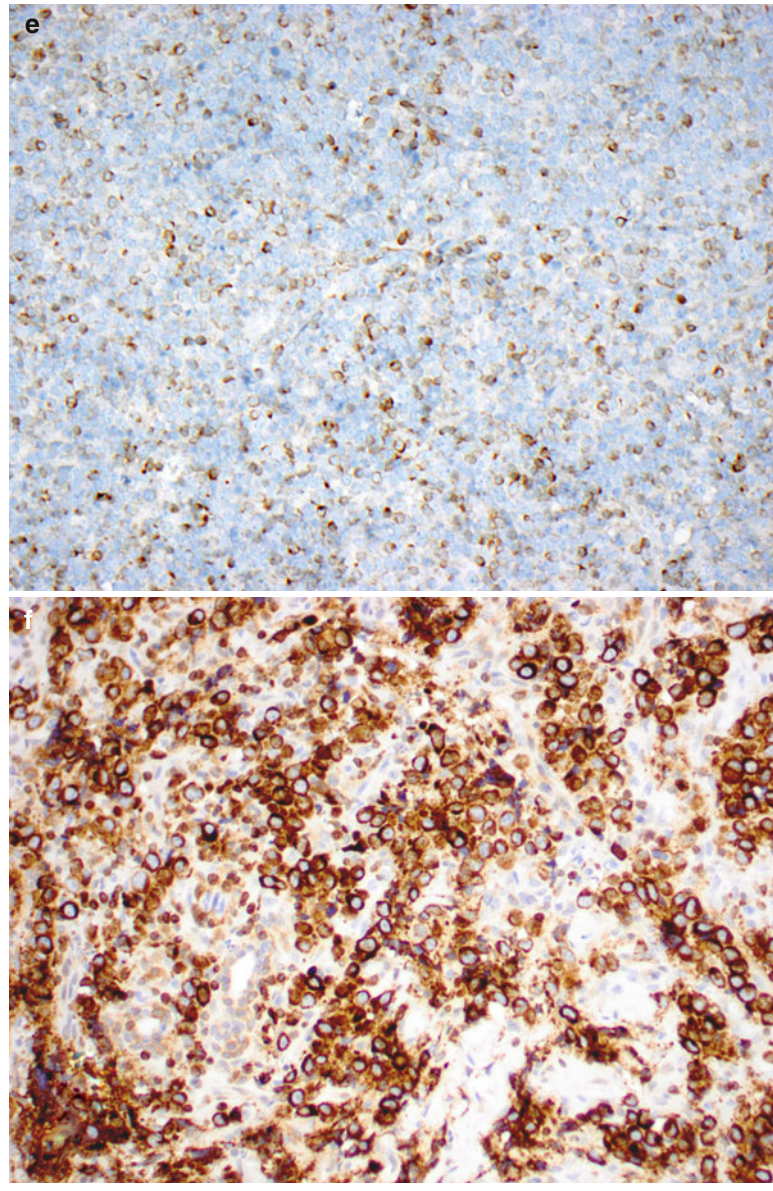

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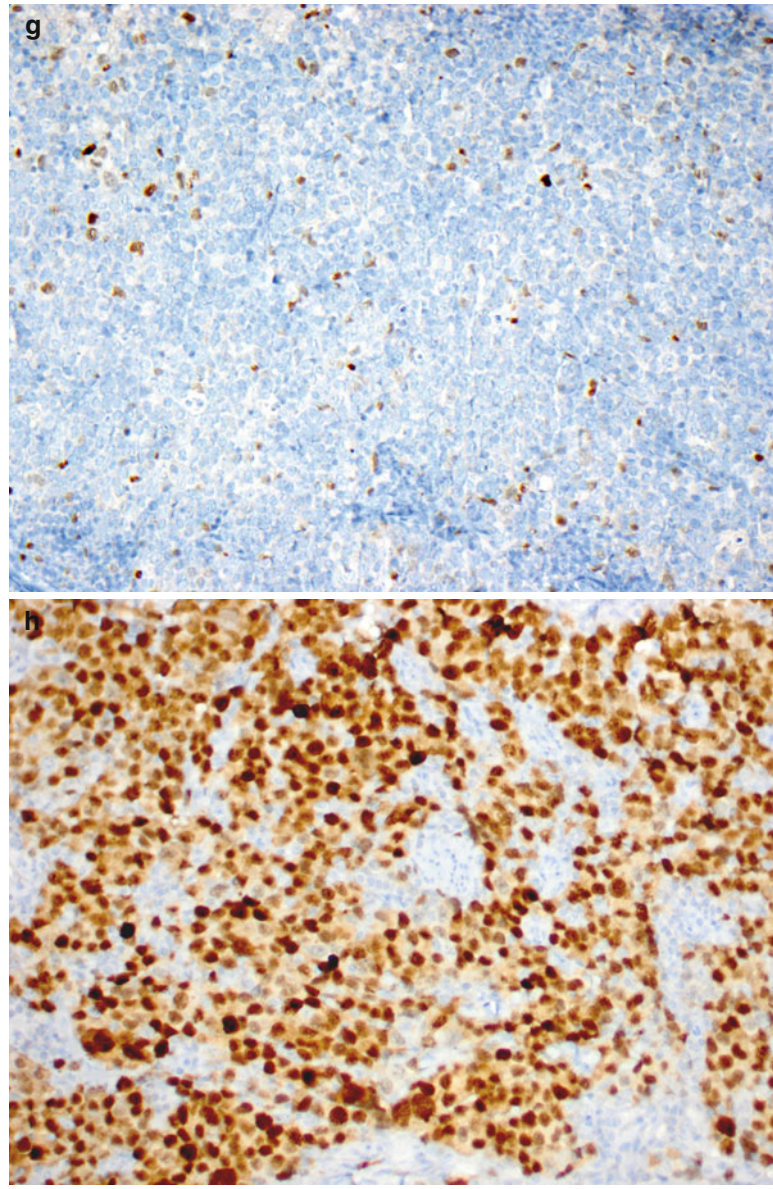

et al. 1998). However, distinguishing these lymphomas through the use of immunohistochemical and molecular markers is of great clinical importance as the 5-year survival of CGD-TCL is much worse than that of SPTCL (11 % versus 82 %, Willemze et al. 2008). Table 3.3 summarizes the immunophenotypes for SPTCL and CGD-TCL. SPTCL expresses a cytotoxic T-cell phenotype: CD3+, CD4−, CD8+, β-F1+, TIA-1+, granzyme B+, and CD56− (Kumar et al. 1998; Hoque et al. 2003; Massone et al. 2004; Willemze et al. 2008; Go and Wester 2004) (Fig. 3.4). While the CD8+ phenotype is vastly predominant for SPTCL, cases of CD4+ CD8− SPTCL have been reported (Kong et al. 2008). CGD-TCL expresses a mature γ/δ T-cell phenotype: CD3+, CD4−, CD8−, β-F1−, TIA-1+, granzyme B+, CD56+ (Massone et al. 2004; Willemze et al. 2005, 2008) (see Fig. 10.36). On frozen section and paraffin (anti-TCR delta) immunohistochemistry, CGD-TCL is positive for TCR gamma-delta, while SPTCL is negative (Willemze et al. 2008; Garcia-Herrera et al.

2011), respectively. TCR gene rearrangement analysis has demonstrated TCR-gamma clonality in approximately 75 % of cases of both SPTCL and CGD-TCL (Willemze et al. 2008). Epstein Barr virus (EBV) testing of either lymphoma is typically negative.

Lupus erythematosus panniculitis also enters into the differential diagnosis. In one-half of the lupus erythematosus panniculitis cases, there are epidermal and dermal changes of discoid lupus erythematosus. In the remaining half there is a predominant subcutaneous pattern with a lymphocytic panniculitis in a lobular pattern with germinal center formation and occasional rimming of adipocytes; thus, in this setting lupus erythematosus panniculitis can mimic the panniculitic lymphomas SPTCL and CGD-TCL (Magro et al. 2001; Aguilera et al. 2007). CD20 is helpful in highlighting clusters or scattered B cells (Massone et al. 2005; Park et al. 2010). The lymphoid infiltrate of lupus erythematosus panniculitis usually comprises a mixture of B and T cells, although a minority of cases (3 of 17 in a study by Park et al.) showed exclusively T-cell infiltrates (Massone et al. 2005; Park et al. 2010). While immunohistochemical studies often show a predominant CD4+ T-cell infiltrate (Park et al. 2010; Massone et al. 2005), others have shown a CD8+ T-cell predominance (Magro et al. 2001) (Table 3.3). Gene rearrangement studies reveal that most lupus erythematosus panniculitis cases exhibit a polyclonal TCR-gamma gene rearrangement, while a small minority of cases showed a monoclonal TCR-gamma gene rearrangement (Park et al. 2010; Magro et al. 2001).

The existence of a borderline diagnosis between lupus erythematosus panniculitis and SPTCL referred to as "atypical lymphocytic lobular panniculitis" and "indeterminate lymphocytic lobular panniculitis" (Magro et al. 2001, 2008) as well as reported cases of SPTCL in patients with systemic lupus erythematosus (Pincus et al. 2009) suggests that there may be a continuous spectrum of disease between lupus erythematosus panniculitis and cutaneous lymphoma. Thus, the integration of clinical findings, histopathologic and immunohisto-

Table 3.2 Immunoprofile of diffuse follicle center cell lymphoma versus cutaneous diffuse large B-cell lymphoma, leg type (Hoefnagel et al. 2003, 2005, 2006; Xie et al. 2008; Senff et al. 2007; Demirkesen et al. 2011; Koens et al. 2010; Pham-Ledard et al. 2010; Kodama et al. 2005)

	Diffuse follicle center cell lymphoma	Cutaneous diffuse large B-cell lymphoma, leg type
CD20	+	+
Bcl2	8–41 %	90–100 %
MUM1	0–50 %	76–100 %
Bcl6	92–100 %	30–100 %
CD10	4–32 %	0–30 %
IgM	0–9 %	100 %
HGAL	88 %	33 %
FOXP1	13 %	100 %

Table 3.3 Immunoprofile of cutaneous γ/δ T-cell lymphoma versus subcutaneous panniculitic T-cell lymphoma versus lupus erythematosus panniculitis (Hoque et al. 2003; Aguilera et al. 2007; Go and Wester 2004; Kong et al. 2008; Massone et al. 2005, 2004, Garcia-Herrera et al. 2011)

	Cutaneous γ/δ T-cell lymphoma	Subcutaneous panniculitic T-cell lymphoma	Lupus erythematosus panniculitis
CD3	+	+	+
CD4	–	–	+
CD8	–	+	– or focally +
CD56	+	–	–
Granzyme B	+	+	–
TIA-1	+	+	– or focally +
βF1	–	+	+
TCRγ	+	–	–
EBER in situ hybridization	–	+ in rare cases (10 %)	–
CD20	–	–	Germinal centers +

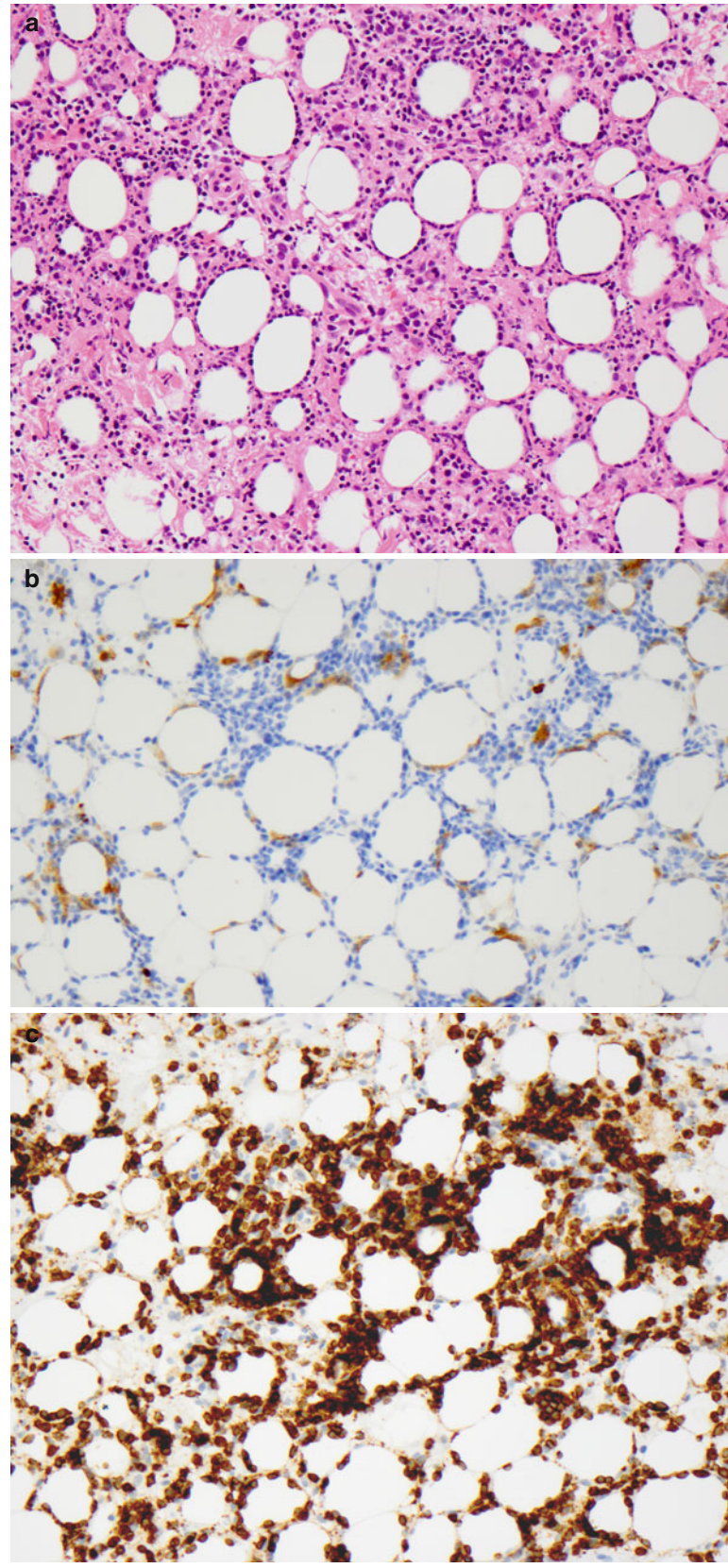

Fig. 3.4 In a case of subcutaneous panniculitic T-cell lymphoma (**a**), negative CD4 (**b**) and strong CD8 (**c**) expression is seen

chemical features, and molecular studies are crucial in correctly classifying these entities. In some instances, long-term follow-up is necessary to understand the biologic course of the disease.

Recommended panel (Table 3.3): CD3, CD4, CD8, CD20, CD56, granzyme B, TIA-1, beta F1, TCRγ, TCR delta, and EBER in situ hybridization

CD30+ Lymphoproliferative Disorders Versus Reactive Processes Versus Lymphoma

CD30 is a member of the tumor necrosis factor superfamily (Schwab et al. 1982). Cutaneous infiltrates of CD30-positive lymphocytes can indicate lymphomatoid papulosis (LyP), anaplastic large cell lymphoma (ALCL) (primary or systemic), rare presentations of Hodgkin's disease, large cell transformation of mycosis fungoides, or a range of nonneoplastic reactive processes (Cepeda et al. 2003; Kempf et al. 2012; Werner et al. 2008; Vergier et al. 2000; Kaudewitz et al. 1989).

The use of anaplastic lymphoma kinase-1 (ALK) and epithelial membrane antigen (EMA) immunostains aids in the distinction between systemic anaplastic large cell lymphoma and cutaneous CD30-positive lymphoproliferative diseases. Whereas cases of systemic ALCL possessing a t(2;5)(p23;q35) translocation between nucleophosmin (*NPM*) gene and anaplastic lymphoma kinase (*ALK*) nearly always demonstrate immunohistochemical positivity for ALK (Cataldo et al. 1999; Perkins et al. 2005), primary cutaneous ALCL and LyP have been demonstrated to be almost always negative for ALK by immunohistochemistry (Yamaguchi et al. 2006) (Fig. 3.5). Furthermore, EMA stains the majority of ALK-positive systemic ALCL cases, but does not usually stain primary cutaneous ALCL (ten Berge et al. 2001) (Fig. 3.5). There have been recent isolated cases of cutaneous ALCL without systemic disease and *cytoplasmic* ALK protein expression and variant translocation reported (Kadin et al. 2008; Su et al. 1997; Sasaki et al. 2004). In addition, a series of six children with a single cutaneous ALK+ ALCL, nuclear-cytoplasmic ALK staining characteristic of the t(2;5) chromosomal translocation was reported (Oschlies et al. 2013).

Distinguishing LyP, primary cutaneous ALCL, and nonneoplastic reactive processes requires careful histopathologic evaluation and clinicopathologic correlation. Primary and secondary cutaneous ALCL often express CD30 in greater than 75 % of tumor cells (Kempf et al. 2011; Plaza et al. 2013). Furthermore, the subtype of LyP (A, B, C, or D) can predict different CD30 staining patterns; while most cases of LyP will show CD30 positivity, the small atypical lymphoid cells with cerebriform nuclei seen in type B LyP have been described as CD30 negative (Kempf 2006). However, others have described CD30-positive type B LyP (Saggini et al. 2010). Recently, several markers including TRAF1 (tumor necrosis factor (TNF) receptor-associated factor), MUM1 (multiple myeloma oncogene 1), Bcl2, and CD15 have been evaluated; however, due to overlapping findings, these markers have not been found to be helpful as diagnostic adjuncts in classifying cutaneous CD30-positive lymphoproliferative disorders (Assaf et al. 2007; Kempf et al. 2008; Paulli et al. 1998; Wasco et al. 2008; Benner et al. 2009) (Table 3.4).

Due to advances in antigen retrieval in immunohistochemistry, CD30 positivity can be detected in a variety of nonneoplastic processes in the skin. Scattered CD30+ cells can be seen in insect and spider bites (Smoller et al. 1992); infections including milker's nodule, Herpes simplex virus infection, molluscum contagiosum, scabies infection, leishmaniasis, and syphilis; lymphomatoid drug eruption (Werner et al. 2008); hidradenitis; pityriasis lichenoides et varioliformis acuta (PLEVA); and various other lesions (Cepeda et al. 2003; Kempf et al. 2012) (see Chap. 12 for differential diagnosis). Some authors report that the CD30+ cells of LyP and ALCL tend to be large, atypical, and sometimes arranged in nests or sheets, while the CD30+ cells of reactive processes tend to be smaller, less atypical, and scattered mostly as single cells (Kempf 2006). Other authors reported clusters of CD30-positive large cells with perinuclear staining in reactive

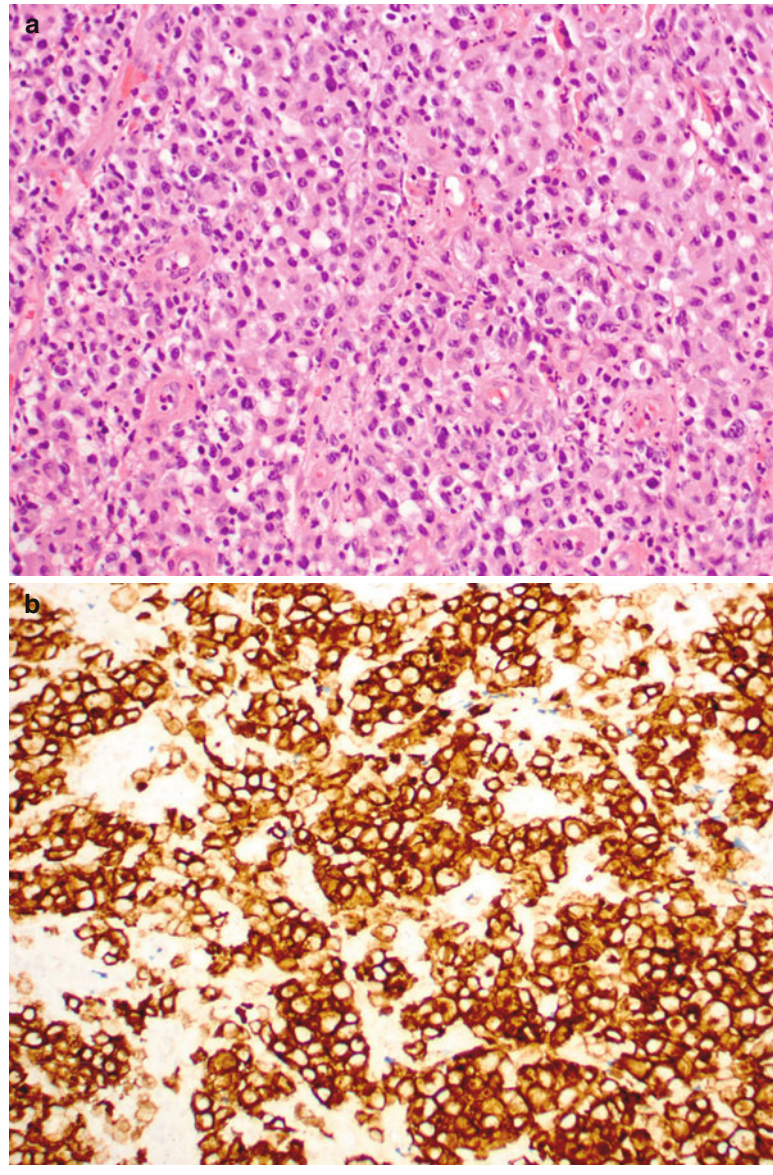

Fig. 3.5 In a cutaneous anaplastic large cell lymphoma (**a**), strong CD30 (**b**) expression is seen while both EMA (**c**) and ALK (**d**) are negative. On the other hand, in a systemic anaplastic large cell lymphoma involving the skin (**e**), strong CD30 (**f**), focal EMA (**g**), and diffuse ALK (**h**) expression is seen

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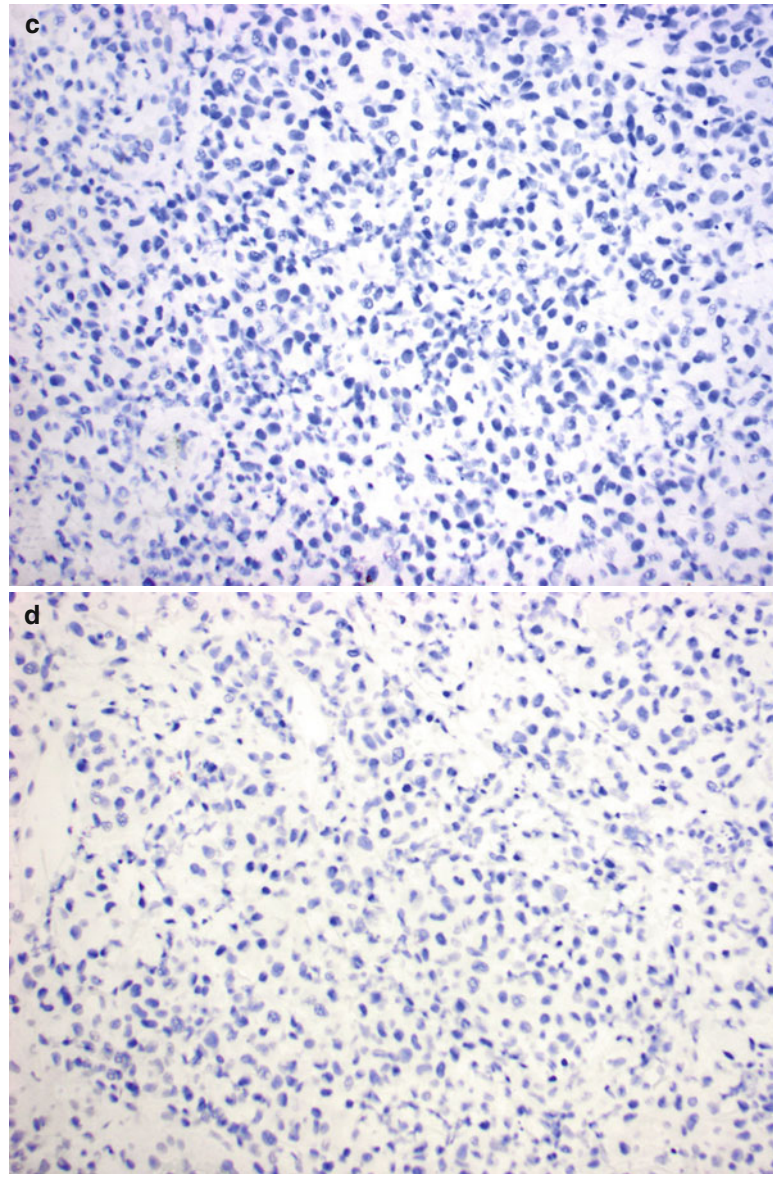

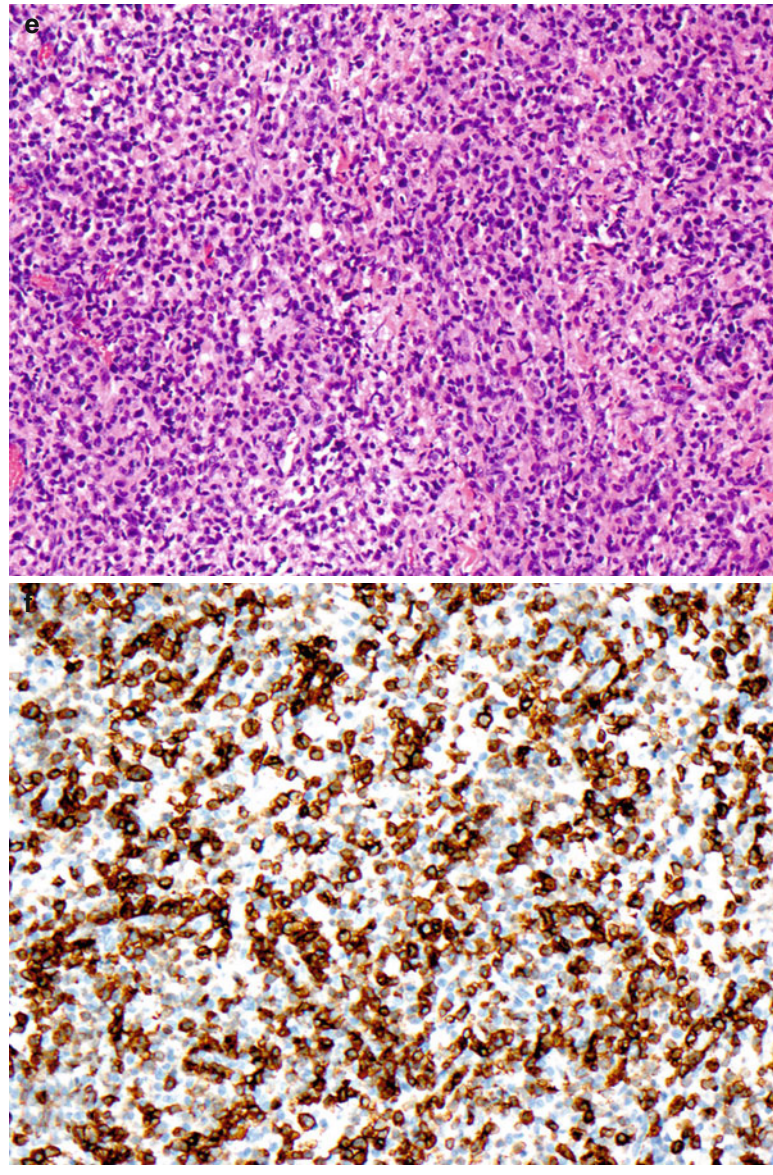

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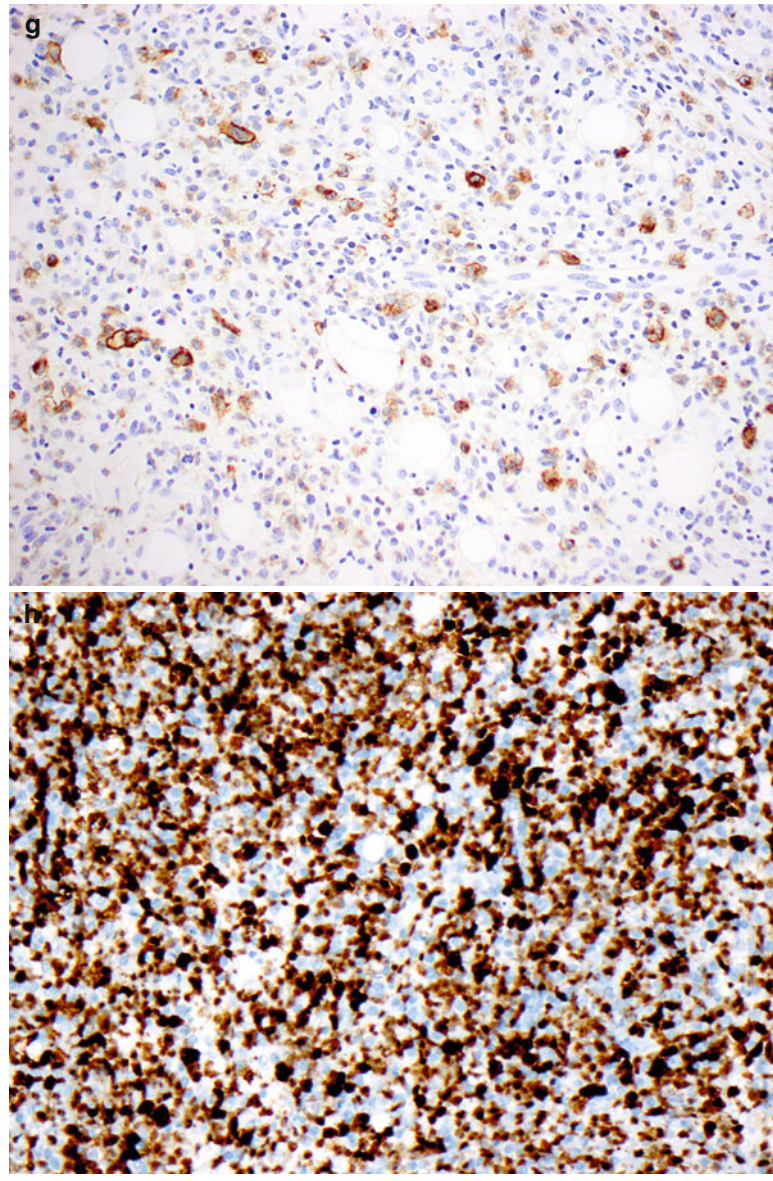


Table 3.4 Immunoprofile of CD30-positive lymphoproliferative disorders versus systemic anaplastic large cell lymphoma versus transformed mycosis fungoides (Kempf et al. 2008; Wasco et al. 2008; Assaf et al. 2007; Benner et al. 2009; Plaza et al. 2013; Kadin et al. 2008)

	Reactive processes	Lymphomatoid papulosis	Cutaneous anaplastic large cell lymphoma	Systemic anaplastic large cell lymphoma	Transformed mycosis fungoides
CD30	Single positive cells	+ <75 %	+ >75 %	+ >75 %	+ >75 %
ALK	–	–	–[a]	+	–
EMA	–	–	–	+	–
MUM1	ND	82–100 %	20–100 %	80–100 %	100 %
TRAF1	ND	84 %	4–87 %	15–50 %	73 %
BCL2	ND	36 %	22 %	38 %	73 %
CD15	ND	18 %	44 %	13 %	9 %

ND not done
[a]Rare cases of cutaneous anaplastic large cell lymphoma with cytoplasmic ALK staining have been reported

processes – a pattern observed in CD30+ lymphoproliferative disorders (Kempf et al. 2008). Cases of PLEVA with CD30-positive cells and monoclonality can be very difficult to distinguish from LyP types B and D (Kempf et al. 2012) (see Chap. 12 for differential diagnosis). Multiple biopsies from lesions with different clinical appearances might be helpful. In the absence of clear differences, histopathologic features diagnostic of a specific reactive process together with clinical correlation may ultimately resolve this diagnostic dilemma.

Recommended panel (Table 3.4): CD30, EMA, and ALK

Follicular Mucinosis Versus Folliculotropic Mycosis Fungoides

In the evaluation of skin biopsies with follicular mucinosis (FM), the distinction between primary follicular mucinosis (PFM) and folliculotropic mycosis fungoides (FMF) with follicular mucin can be challenging and requires attention to clinical information and histopathologic, immunohistochemical, and TCR gene rearrangement studies. Follicular mucinosis can be idiopathic/primary or secondary, occurs mainly in children and young adults, and is not associated with other cutaneous or systemic disorders (Cerroni et al. 2002). These lesions are typically localized and spontaneously regress, though some may be persistent (Gibson et al. 1989; Hempstead and Ackerman 1985; Brown et al. 2002). The secondary form of follicular mucinosis may be an epiphenomenon in a variety of conditions including arthropod assault, lupus erythematosus, eosinophilic folliculitis, as well as cutaneous T-cell lymphoma (Hempstead and Ackerman 1985; Gerami et al. 2008; Cerroni et al. 2002; Rongioletti et al. 2010). Lymphoma-associated follicular mucinosis consists primarily of mycosis fungoides (MF) and its variant folliculotropic mycosis fungoides (FMF) (Gerami et al. 2008; Burg et al. 2005). In some instances, follicular mucinosis may be the first presentation of lymphoma (Cerroni et al. 2002).

The typical immunoprofile of MF is a CD2+, CD3+, CD4+, CD5+, CD45RO+, CD8−, TCRβ+, and CD30− (Burg et al. 2005). Folliculotropic MF is an uncommon variant of MF with distinctive clinical features, histologic findings, and prognosis, but with identical immunophenotypic and molecular findings as classic MF (Bonta et al. 2000; van Doorn et al. 2002; Gerami et al. 2008). While CD4+ predominance is seen in MF, the majority of cases of primary follicular mucinosis exhibited equivalent numbers of CD4+ and CD8+ lymphocytes (Rongioletti et al. 2010) (Fig. 3.6). Whereas cases of lymphoma-associated follicular mucinosis often exhibit loss of T-cell markers (CD2, CD5), loss of T-cell marker expression would not be expected in the setting of primary follicular mucinosis (Burg et al. 2005; Bonta et al. 2000). Histochemical techniques, including periodic acid-Schiff, colloidal iron, and Alcian blue at pH 2.5 and 0.5, have not been found to be helpful in distinguishing the mucin deposits of PFM and LAFM (Rongioletti et al. 2010). Since clonal TCR gene rearrangement has been detected in a subset of cases of presumed primary follicular mucinosis (Bonta et al. 2000; Brown et al. 2002; Rongioletti et al. 2010; Zelickson et al. 1991; Cerroni et al. 2002), the presence of clonal TCR gene rearrangement does not allow for definitive distinction between primary follicular mucinosis and lymphoma-associated follicular mucinosis. Ultimately, the proper classification of FM as either PFM or FM associated with MF depends on careful consideration of clinical, histopathologic, immunophenotypic, and molecular parameters. Furthermore, some cases of FM may not lend themselves to straightforward classification (see Chap. 4 for discussion of the spectrum of FM, FM dyscrasia, and folliculotropic MF).

Recommended panel: CD2, CD3, CD5, CD4, and CD8

Lymphomatoid Drug Eruption Versus Mycosis Fungoides

In some instances, it is difficult to distinguish mycosis fungoides from lymphomatoid drug reaction, a delayed type hypersensitivity reaction that shares histologic features with MF. One important similarity is involvement of the epidermis by clusters of lymphocytes. This epidermotropism has

specifically been noted to target sites of preferential antigen processing, such as the suprapapillary plates, acrosyringea, and hair follicles. Other shared traits may include loss of CD7 on immunohistochemistry and even clonal T-cell receptor gene rearrangements (Magro and Crowson 1996; Murphy et al. 2002; Florell et al. 2006). Since loss of CD7 is commonly seen in a variety of inflammatory disorders (Murphy et al. 2002), partial loss of CD2 or loss of multiple T-cell antigens would be helpful in diagnosing peripheral T-cell lymphoma (Michie et al. 1989; Ormsby et al. 2001; Florell et al. 2006). An elevated CD4:CD8 and low CD8:CD3 ratios have been reported to be helpful in diagnosing mycosis fungoides (Florell et al. 2006; Ortonne et al. 2003). In the setting of MF, more CD4+ lymphoid cells are seen in the epidermis. On the contrary, more CD8+ lymphoid cells are seen in the epidermis in the setting of lymphomatoid drug reaction (Fig. 3.7).

Recommended panel: CD2, CD3, CD5, CD4, andCD8

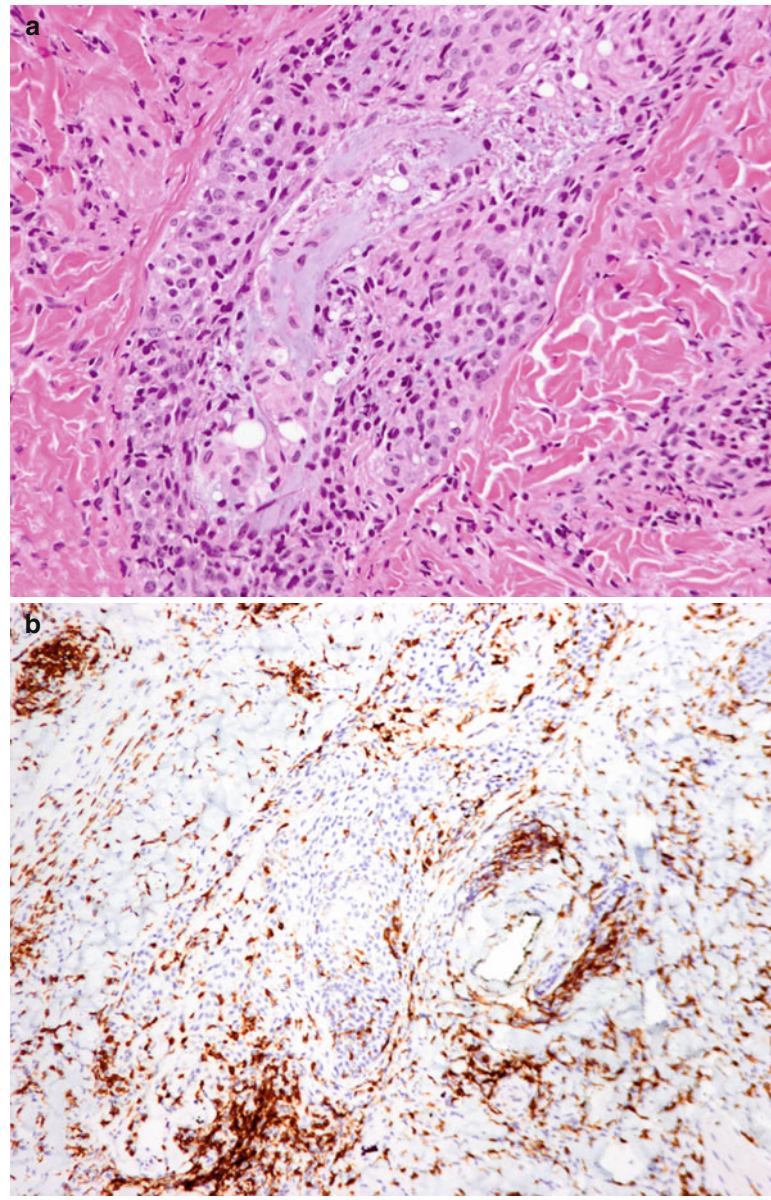


Fig. 3.6 In a case of follicular mucinosis (**a**), the lymphoid infiltrate is positive for CD3 (**b**) and without an increase in the CD4 (**c**) to CD8 (**d**) ratio. On the contrary, in a case of follicular mycosis fungoides (**e**), the lymphoid infiltrate highlighted by CD3 (**f**) is predominantly CD4 positive (**g**) in comparison to CD8 (**h**)

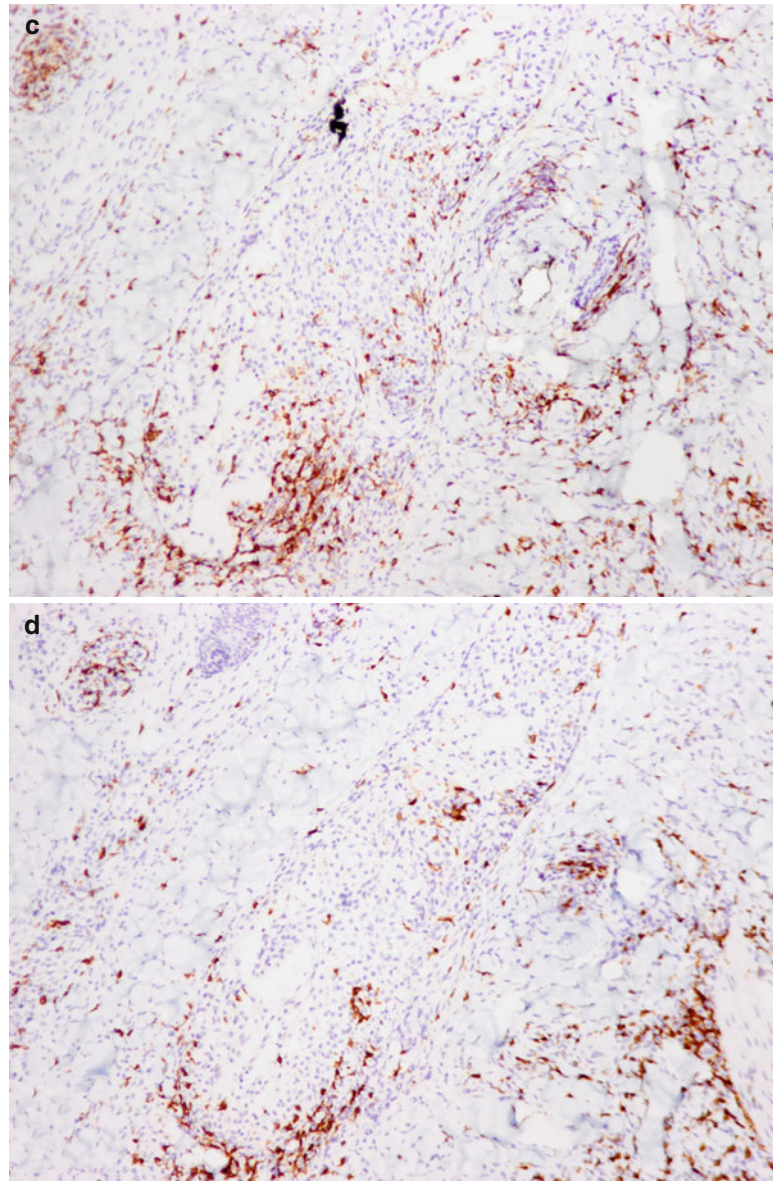


Fig. 3.6 (continued)

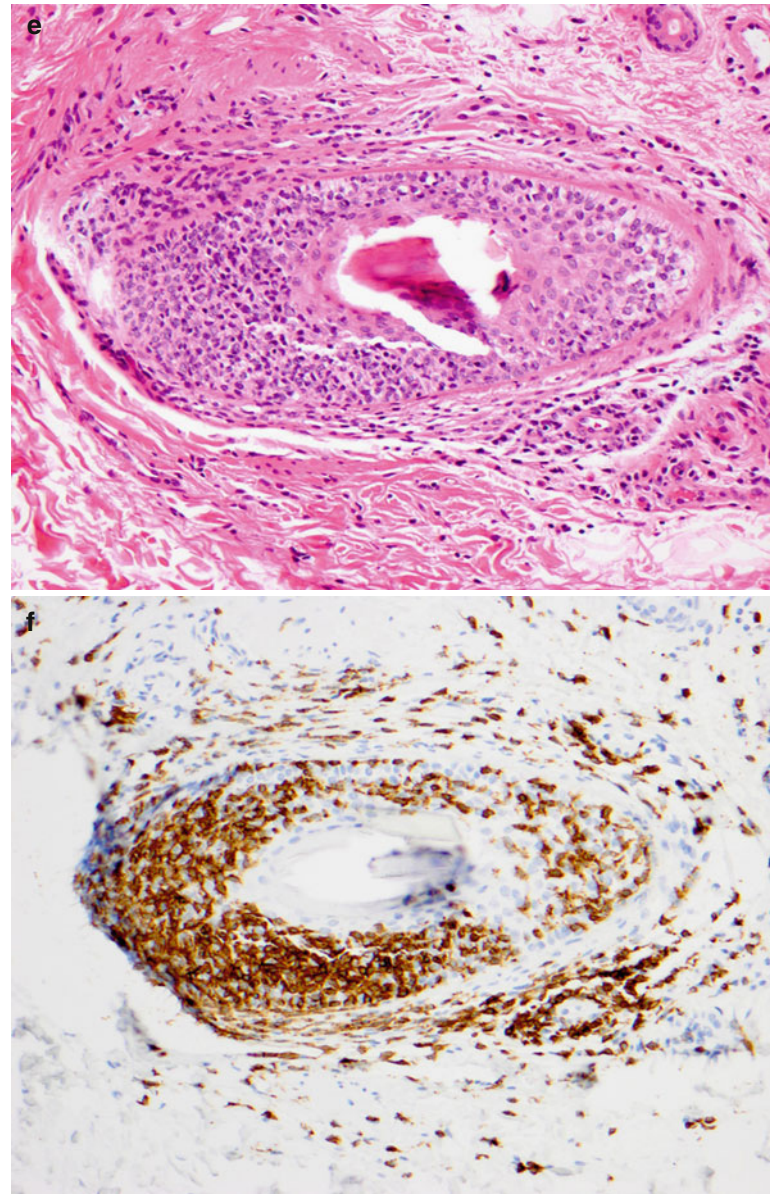
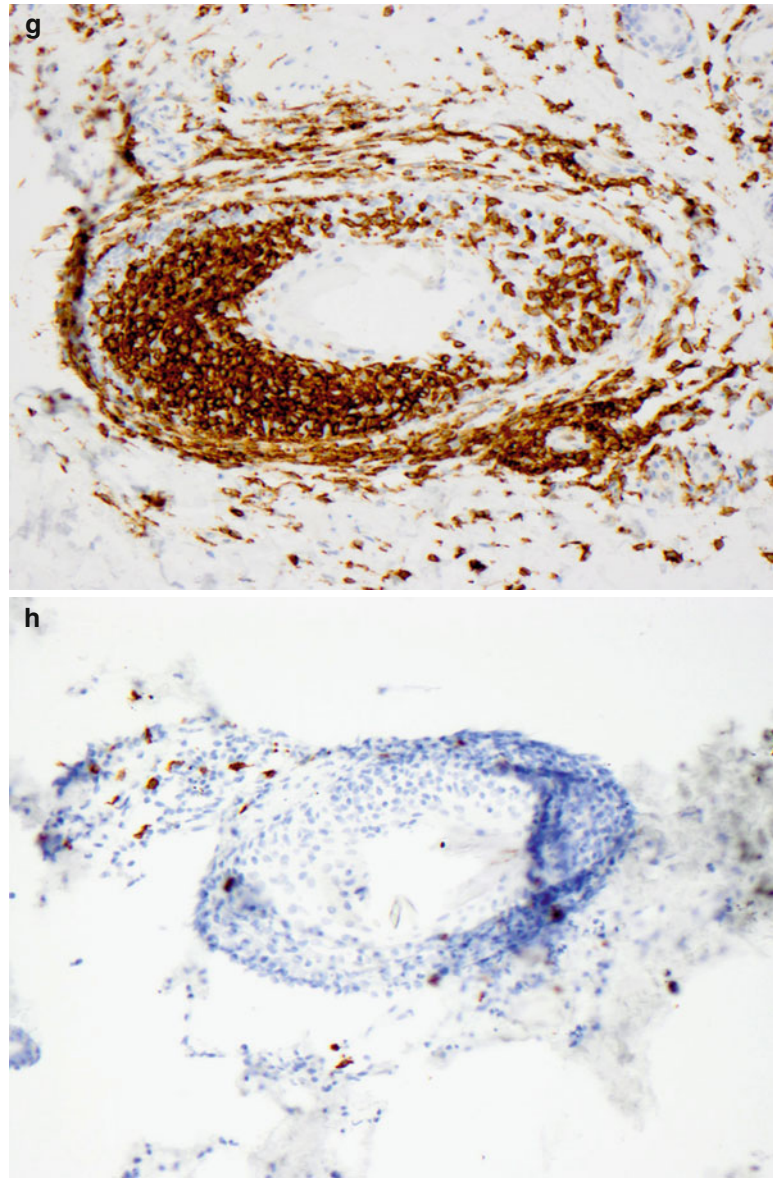


Fig. 3.6 (continued)



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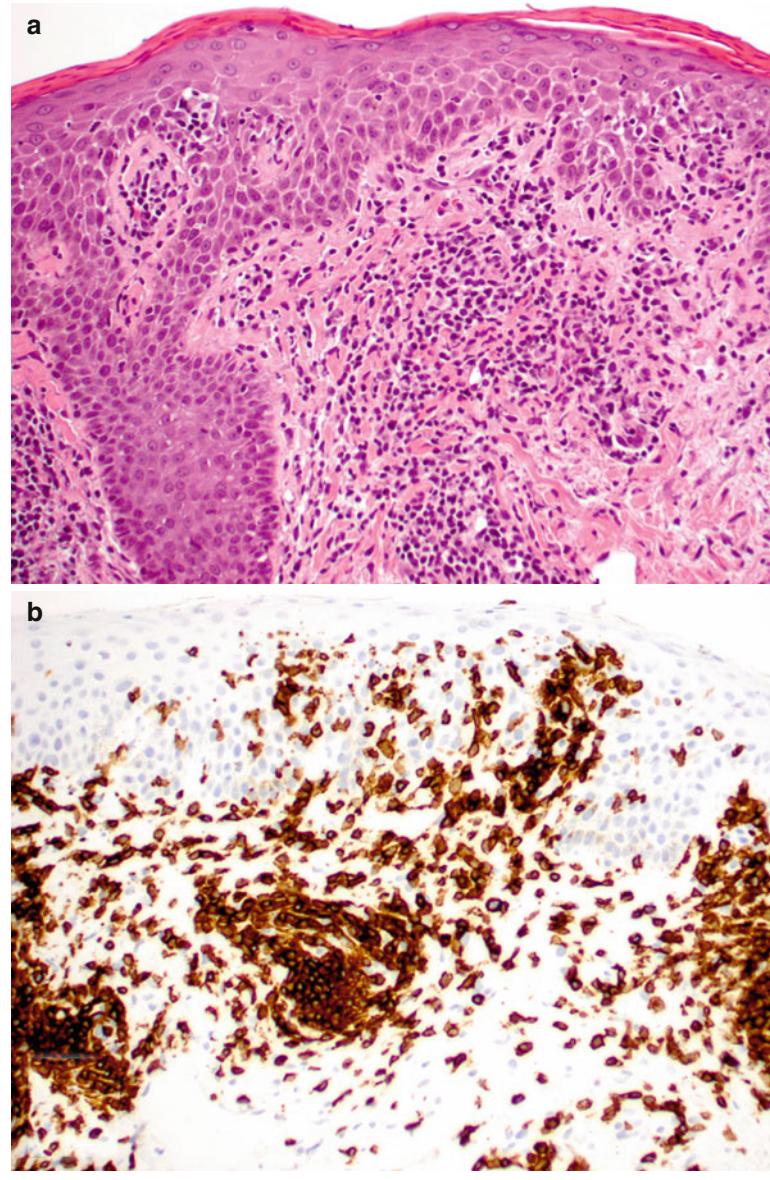

Fig. 3.7 In a case of lymphomatoid drug eruption (**a**), the lymphoid infiltrate within the epidermis is CD3 positive (**b**) and with a decrease in the CD4 (**c**) to CD8 (**d**) ratio. On the other hand, in a case of plaque-stage mycosis fungoides (**e**), the intraepidermal atypical lymphoid cells are CD3 positive (**f**) and predominantly CD4 positive (**g**) in comparison to CD8 (**h**)

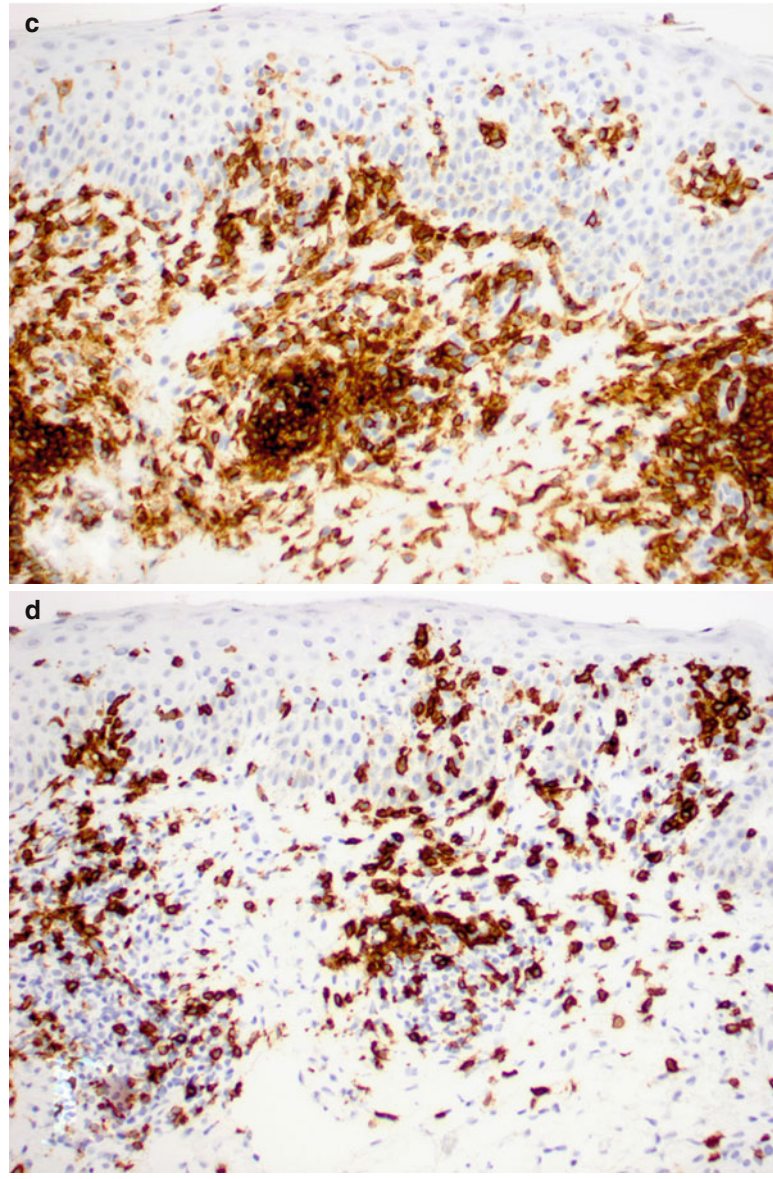

Fig. 3.7 (continued)

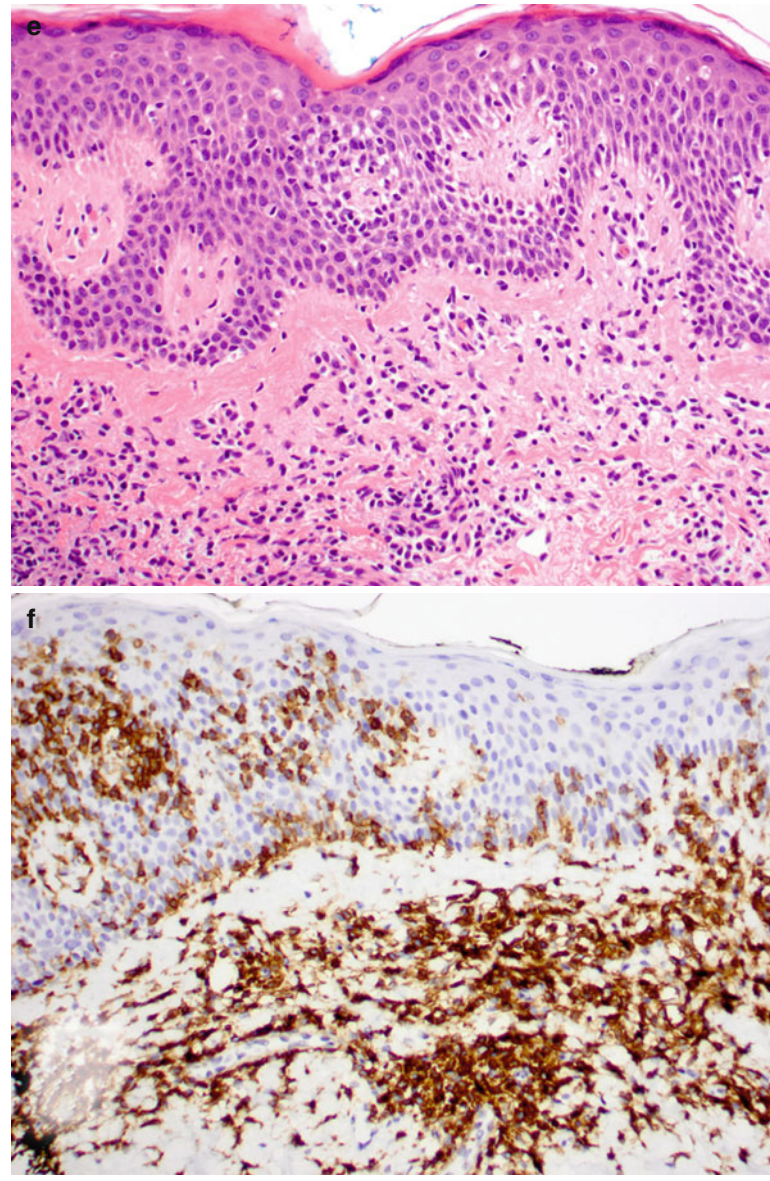

Fig. 3.7 (continued)

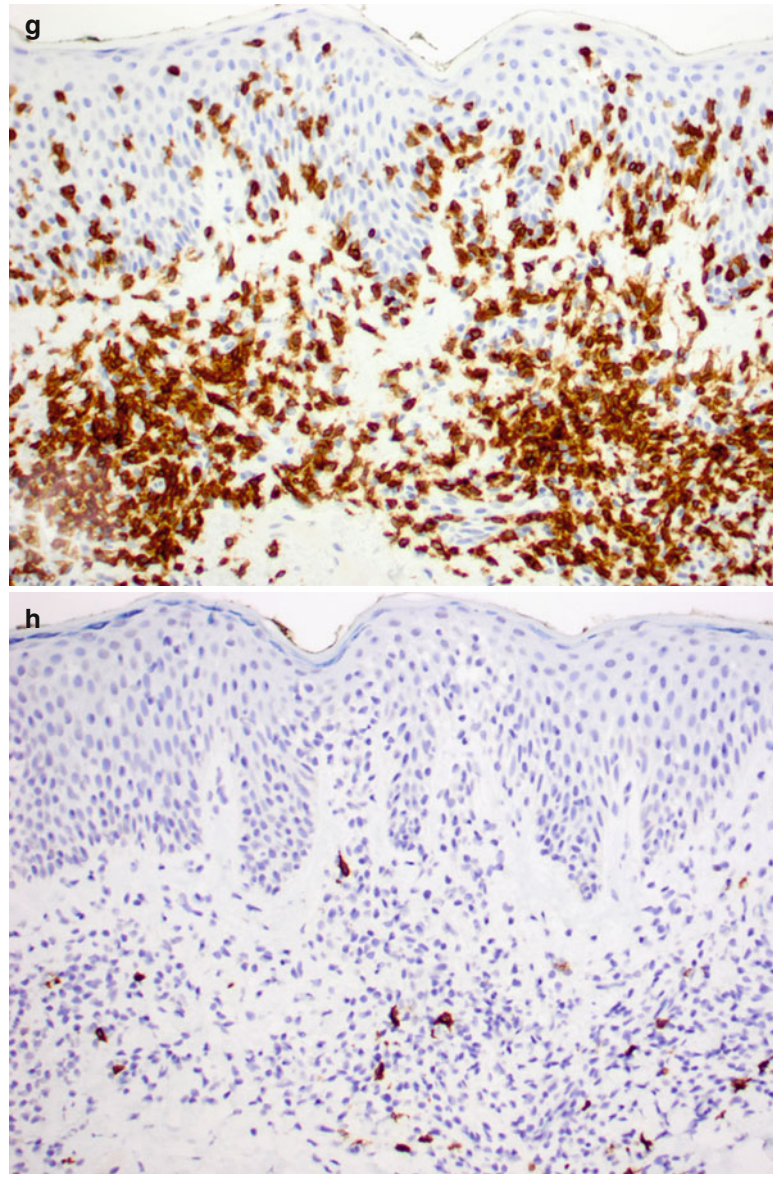

Fig. 3.7 (continued)

Table 3.5 Selected diagnostic immunohistochemical panels

	Recommended immunohistochemical panel
Reactive lymphoid hyperplasia versus low-grade B-cell lymphoma	CD3, CD20, Bcl2, Bcl6, CD21, kappa, lambda in situ hybridization
Diffuse follicle center cell lymphoma versus cutaneous diffuse large B-cell lymphoma, leg type	CD20, Bcl2, Bcl6, IgM, MUM1
Subcutaneous panniculitic T-cell lymphoma versus cutaneous gamma-delta T-cell lymphoma	CD3, CD4, CD8, CD56, granzyme B, TIA-1, TCR beta F1, TCR gamma
Cutaneous CD30+ lymphoproliferative disorder versus systemic anaplastic large cell lymphoma	CD30, EMA, ALK
Follicular mucinosis versus folliculotropic mycosis fungoides	CD2, CD3, CD4, CD5, CD8
Lymphomatoid drug reaction versus mycosis fungoides	CD2, CD3, CD4, CD5, CD8

TCR T-cell receptor

Summary

In the diagnosis of lymphoid infiltrates, a panel of immunohistochemical markers can be helpful in narrowing the differential diagnoses (Table 3.5). It would be best to establish a differential diagnosis based on clinical and histologic evaluation, order a panel of immunohistochemical stains, and then interpret the stains with the differential diagnosis in mind.

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