Chapter 15
CD30+ Diseases

Anaplastic Large-Cell Lymphoma and Lymphomatoid Papulosis

Peter Borchmann

15.1 Introduction

The CD30 antigen was first detected in 1982 using a Hodgkin-Reed/Sternberg (H-RS) cell line and it was cloned and characterized as a member of the tumor necrosis factor (TNF) receptor superfamily a decade later in 1992 (1–3). Soon it became clear that, although restricted to hematopoietic cells, it was not only expressed by H-RS cells but also by activated T- and B-cells and some other lymphoid malignancies. In addition to Hodgkin's lymphoma (HL), the following primary systemic lymphomas also express CD30: anaplastic large-cell lymphoma (ALCL) in all cases, the majority of posttransplant lymphoproliferative disorders (PTLDs, see Chapter 12), the primary mediastinal B-cell lymphoma with a comparably weak CD30 expression (see Chapter 10), and the lymphomatoid granulomatosis (Lyg) in some instances (see Chapter 11). In addition, CD30 is expressed in primary cutaneous CD30-positive T-cell lymphoproliferative disorders, to which the primary cutaneous ALCL (C-ALCL), the lymphomatoid papulosis (LyP), and the borderline lesions belong.

This chapter will focus on the systemic ALCL and the primary cutaneous CD30-positive T-cell lymphomas, although CD30 is expressed by many others of the rare lymphoid malignancies. Because CD30 is the red thread for this chapter, this receptor will be described more in detail first.

15.2 The CD30 Antigen

CD30 belongs to the TNF-R superfamily, which consists of 26 receptors and 18 ligands known so far (4). These receptors are characterized by the presence of 40-amino-acid, cysteine-rich repeats in their extracellular domains. CD30 is the largest TNF-R with six of these motifs in its extracellular domain (see Figure 15.1) (5). The whole protein has a molecular weight of 120 kDa and is a type I transmembrane protein. The extracellular part of CD30 can be shed by metalloproteinases and is then released into the plasma. This soluble CD30 (sCD30) is an ~90-kDA

S.M. Ansell (ed.), *Rare Hematological Malignancies.*

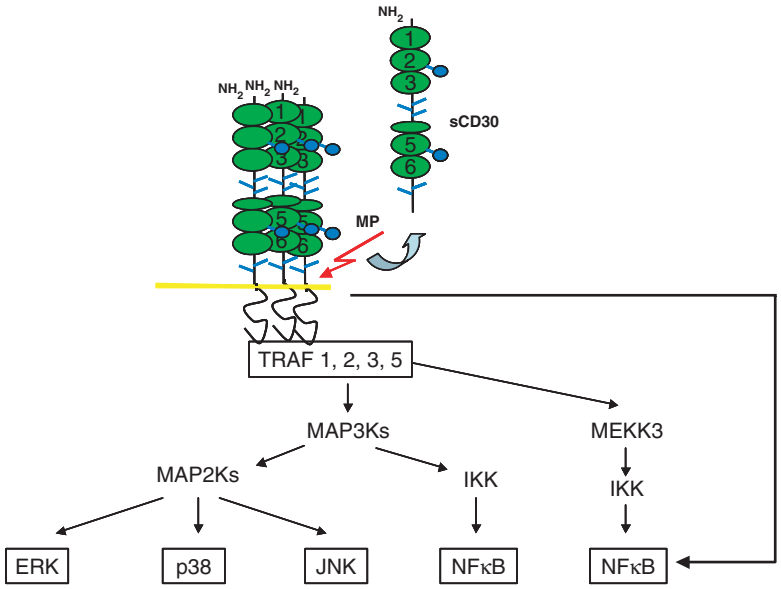

Figure 15.1 The CD30 antigen and its signal transduction

protein that can be found in the sera of patients with CD30-positive lymphoid malignancies, with autoimmune diseases or with acute or chronic viral infections, especially during infection with the Epstein-Barr virus (EBV).

CD30 signaling is induced by its trimerization. Physiologically, aggregation of CD30 is mediated by binding to its counterpart, the CD30 ligand (CD30L, CD153). In contrast to other TNF-Rs, CD30 contains no intracellular death domain (DD), which could cause the cell death upon receptor activation. CD30 acts via so-called TRAFs (TNF receptor-associated factors). So far, six TRAFs are known and the cytoplasmatic tail of CD30 interacts through its binding sites with four of them: TRAF-1, -2, -3, and -5. Trimerisation of CD30 thereby leads to the activation of different pathways, including extracellular signal-regulated kinase (ERK), c-jun amino terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), and NF-κB (nuclear factor-κB) (see Figure 15.2). This can then result in the secretion of cytokines, including interleukin (IL)-2, IL-6, IL-8, IL-12, and granulocyte colony-stimulating factor (G-CSF). Based on these diverse possibilities of intracellular signaling, CD30 activation can have pleiotropic and even opposing effects for the cell, ranging from proliferation induction and enhanced cell survival over growth arrest to induction of apoptosis. CD30 deficiency does not result in overt defects in either the T-cell or the B-cell homeostasis. CD30 has been reported to control thymic negative selection, but this could not be confirmed in a more recent study with CD30–/– mice (6). Some studies have shown that CD30L/CD30 might provide proliferation and/or survival signals to allow the generation of high numbers

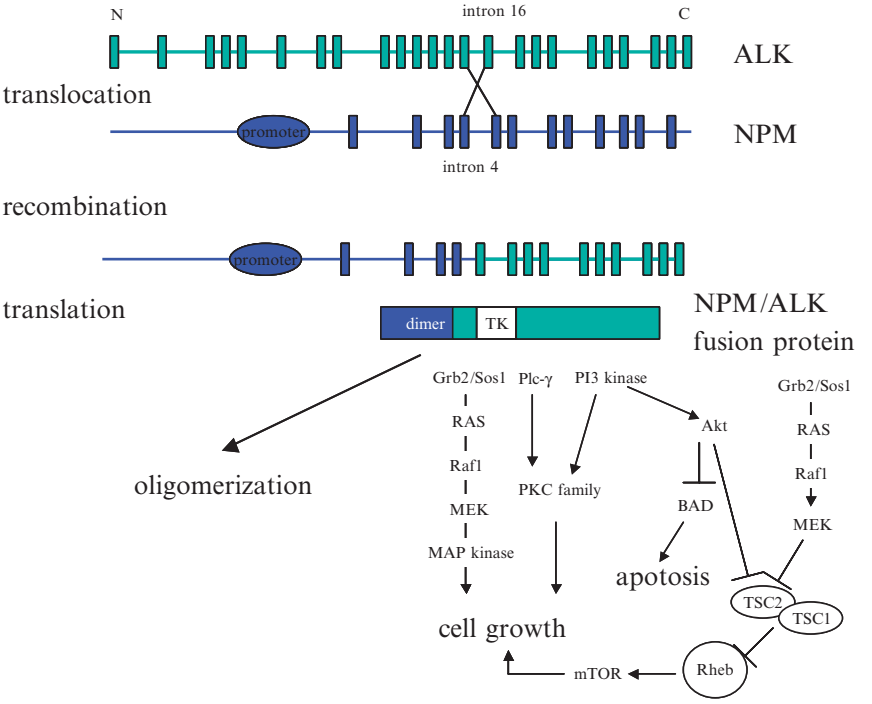

Figure 15.2 The NPM/ALK fusion protein. TSC: tuberous sclerosis complex proteins. (Adapted from Ref. 23)

of antigen-specific T-cells (7, 8). Adoptive transfer of antigen-specific CD8 T-cells into CD30L–/– mice resulted in defective primary and secondary expansion after challenge with antigen. So far, no human diseases have been linked with defects of the CD30 genes (1p36 for CD30 and 9q33 for CD30L), which might be interpreted as a further hint that CD30 is more likely to play a role in the fine-tuning of the immune system, as described earlier.

In malignant cells, the overexpression of CD30 (e.g., by H-RS cells in HL) can lead to self-aggregation, recruitment of TRAF-2 and TRAF-5, NF-κB activation, and strong pro-proliferative signals. Therefore, CD30 was thought to have a critical role in the malignant phenotype of H-RS and ALCL cells. Recent studies suggest that CD30 overexpression is not the driver lesion but is caused by constitutive expression of transcription factors belonging to the AP-1 family, in particular JunB (9). Interestingly, in cases of primary cutaneous CD30-positive LyP showing coexpression of CD30 and CD30L, spontaneous regression has been frequently observed, suggesting a causal relationship (10). This observation suggests pro-apoptotic effects under specific conditions.

15.3 Anaplastic Large-Cell Lymphoma

It is now two decades ago that large-cell lymphomas with anaplastic morphology were first described as an entity by Stein and colleagues (11). This novel lymphoma category was defined by large pleomorphic blasts and the CD30 overexpression on all neoplastic cells. Despite these common features, heterogeneity in the cytology and in the antigen profile of the tumor cells, as well as in the clinical features of patients affected by this condition, was noticed in the original description and led to the distinction of several morphologic, immunophenotypic, and clinical subforms of ALCL, as reviewed by Stein et al. recently (12). For practical reasons, in this chapter we will classify the different ALCLs with reference to their origin (T- or B-cell) and clinical presentation (primary systemic vs. primary cutaneous; see Table 15.1). Also for practical reasons, the primary cutaneous ALCL will be described together with the lymphomatoid papulosis under the chapter heading "primary cutaneous CD30 positive T-cell lymphoproliferative disorders", as both are obviously closer related to each other than to the systemic form of CD30 positive T-cell lymphomas.

15.3.1 Primary Systemic ALCL

About 60% of all primary systemic ALCL are positive for the "anaplastic lymphoma kinase" (ALK) (see Table 15.1) (13–15). The remaining cases are either ALK-negative T-cell ALCL or of B-cell origin. Morphologic analysis and immunohistochemical staining can further subclassify systemic ALCL into the *common* (or classic) subtype, the *small cell*, and the *lymphohistiocytic* ALCL. The common type is ALK-positive in about 60–85% of all cases, whereas the small-cell and the lymphohistiocytic ALCL are positive in nearly all cases. The common type is characterized by sheets of large lymphoid cells with chromatin-poor horseshoe-shaped nuclei that contain

Table 15.1 ALCL classification system

ALCL				
B-cell[a]	**T-cell[b]**			
	Primary systemic ALCL		Primary cutaneous CD30-positive T-cell lymphoproliferative disorders	
	ALK-positive[c]	ALK-negative	ALCL-like	Lymphomatoid papulosis

[a]Mostly EBV latent membrane antigen-positive, ALK-negative, often HIV-related lymphoma, accounting for ~15% of all cases.

[b]EBV-negative, sometimes not expressing T-cell antigens (null-cell), but clonally expression of rearranged TCR β and γ genes is detectable in 90% of cases of T-cell and null-type (55). Up to a third of all cases express cytotoxic molecules, indicating NK-cells as possible precursors in some cases.

[c]Representing 60% of all cases.

multiple nucleoli. These are the so-called "hallmark cells," because they can be found in all ALCL variants, including the small-cell and lymphohistiocytic subtypes (16). The small-cell variant is characterized by a mixture of small, medium-sized, and large lymphoid cells (17). Additionally, there are the following rare subtypes: the *giant cell-rich*, and the *Hodgkin-like* ALCL. In both, ALK overexpression is found only in a minority of cases (~40% in giant cell-rich and ~15% in Hodgkin-like ALCL). In the WHO (World Health Organization) classification though, Hodgkin-like ALCL is not considered to be a "real" entity, as ALCL is a T-cell lymphoma and HL is a B-cell lymphoma in almost all cases. This has been confirmed in difficult cases by antigen-receptor gene rearrangement analysis. Due to the expression of cytotoxic molecules in about 30% of all cases, the postulated cell of origin is an activated mature cytotoxic T-cell for the primary systemic ALCL.

15.3.2 The Role of ALK in ALK-Positive ALCL

Soon after the first description of anaplastic large-cell lymphomas as a distinct entity, an association with a balanced (2;5)(p23;q35) chromosomal translocation was reported from different groups (18–21). As a result of this translocation, an 80-kDa fusion protein containing the ALK tyrosine kinase linked to the NPM (nulcleophosmin) N-terminal dimerization domain arises (see Figure 15.2). The fusion gene NPM/ALK is under control of the ubiquitously active NPM promoter, resulting in an overexpression of the NPM/ALK protein.

Anaplastic lymphoma kinase is a member of the insulin receptor superfamily receptor tyrosine kinase and is a 205-kDa type I transmembrane glycoprotein. ALK is physiologically expressed only within the developing and mature nervous system, but not in normal lymphoid cells. As with CD30 (see earlier section), ALK knockout mice develop without major abnormalities, indicating no essential role for this kinase.

Normal NPM is a 37-kDa phosphoprotein that is physiologically highly expressed during embryogenesis. NPM plays a role in ribosome assembly and protein synthesis. Accordingly, the expression of NPM is increased when cell division and growth are stimulated. It is active as a homohexamer that shuttles ribonuclear complexes between the nucleolus and the cytoplasm.

Consequently, the NPM/ALK fusion protein forms oligomers in the nucleus and cytoplasm of NPM/ALK-expressing cells, causing a constitutive activation of the ALK tyrosine kinase, also indicated by its heavily phosphorylated tyrosine residues (22, 23). This constitutive tyrosine kinase activation certainly plays a major role in the malignant phenotype of ALK-positive ALCL. Although not fully understood, activation of phospholipase C (PLC)γ, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), STAT3, STAT5, and mitogen-induced extracellular kinase (MEK)/ERK have been shown to be involved in the malignant phenotype in NPM/ALK-expressing cell lines (see Figure 15.2). In addition, mTOR (mammalian target of rapamycin) activation might play a major role, as recent research suggests. As

shown in Figure 15.2, the NPM/ALK-generated signal is transmitted through the MEK/ERK and, to a much lesser degree, the PI3K/Akt pathways. In addition, mTOR also appears to participate in this signaling cascade. Interestingly, the mTOR inhibitor rapamycin profoundly suppresses proliferation and enhances the apoptotic rate of ALK-positive ALCL cells. Thus, activation of the rapamycin-sensitive mTOR signaling pathway might be a new mechanism by which NPM/ALK promotes malignant transformation (24).

On the other hand, activated ALK is probably not sufficient to transform otherwise normal lymphoid cells, as indicated by several observations. In ALK transgenic mice, tumors occur only in a subset of animals and, in addition, this takes a rather long time (25). In addition, several studies using polymerase chain reaction (PCR) tests have detected ALK fusion genes in reactive lymphoid tissues and peripheral blood of healthy individuals (26). This might explain why ALK rearrangements have been found in various diseases. So far, the secondary events that collaborate with ALK in malignant transformation are not known.

In the meantime, many other translocations involving the ALK gene have been detected; they are listed in Table 15.2. Of these, the TFG and the TPM3 proteins also contain dimerization regions. Thus, they can spontaneously form homodimers of x-ALK proteins to mimic ligand binding. Again, this results in the constitutive activation of the ALK kinase domain and certainly has an oncogneic capacity. Interestingly, these different fusion proteins exhibit different growth kinetics with regard to colony formation in soft agar, invasion, migration through the endothelial barrier, and tumorigenicity, again underscoring the importance of the different ALK-containing fusion proteins for the malignant phenotype (27)

15.3.3 The Role of CD30 in ALK-Positive ALCL

Although these ALCLs all express the CD30 antigen at very high levels, the role of this overexpression for the malignant phenotype remains unclear. Obviously, in

Table 15.2 x-ALK fusion genes

Gene	Chromosomal location	Frequency in ALK-positive ALCL (%)	Size of fusion protein (kDa)	Localization of fusion protein
Nucleophosmin, NPM	5q35	75	80	Cytoplasmic, nuclear, nucleolar
Tropomyosin 3, TPM3	1q21	15	104	Membranous and diffuse cytoplasmic
TRCK fusion gene, TFG	3q21	2	85, 97	Diffuse cytoplasmic
ATIC	2q35	2	96	Cytoplasmic
Clathrin heavy chain, CLTC	17q23	2	250	Punctate cytoplasmic
Moesin, MSN	Xq11-12	1	125	Plasma membrane

ALCL cell lines such as Karpas 299, CD30 trimerization can induce apoptosis. However, under conditions in which new protein synthesis is blocked, the ability of CD30 to trigger cell death in ALCL cell lines is substantially enhanced. Furthermore, CD30-induced cell death in ALCL cells can be inhibited by the pan-caspase inhibitor zVAD-fmk, suggesting that CD30 triggers cell death by an apoptotic pathway. These data suggest that CD30 induces *de novo* synthesis of a survival protein(s) that blocks its cell-death-promoting activity (28). Anti-CD30 antibodies can transduce this signal only if they are hyper-cross-linked, and even then, binding by the natural ligand CD30L is more efficient (29). Taken together, although CD30 can induce apoptosis in ALCL, this does not occur on a regular basis and the factors contributing to these different effects are not yet known. Recent results indicate that this might be due to the activation of the p38 MAP kinase pathway (29) due to the fact that pharmacologic inhibition of p38 MAPK unmasked a CD30-triggered apoptotic pathway involving caspase-8. Additionally, the DD-containing adaptor protein FADD seems to be involved in the signal transduction and might be activated by TNFR1, as CD30 does not contain a DD and therefore cannot activate FADD directly.

15.3.4 Clinical Aspects of Primary Systemic ALCL

15.3.4.1 Clinical Features and Prognosis

There is evidence that the clinical features and prognosis of systemic ALCL differ significantly depending on the presence of x-ALK fusion proteins. ALK-positive ALCL occurs mostly in the first three decades, whereas ALK-negative ALCL shows the highest incidence in the sixth decade. For ALK-positive cases, there is a strong male predominance (male/female ratio: 6.5:1), which is completely missing in ALK-negative patients (see Figure 15.3A). The prognosis for ALK-negative patients is much poorer, with a median overall survival of about 2 years (30). In contrast, long-term survival is seen in ALK-positive patients in almost 75% (see Figure 15.3B). This prognostic difference between ALK-positive and ALK-negative patients was first described by Shiota and colleagues, and then confirmed by two larger series. These studies could also show that the survival difference does not depend on the different age at first diagnosis (14, 31, 32). In these studies, the 5-year overall survival of ALK-positive versus ALK-negative ALCL was 71% versus 15% in one study and 79% versus 46% in the other. New prognostic markers as MUC-1 are also becoming apparent (33). In ALK-positive patients, the 5-year progression-free survival (PFS) rate was 52% in those who were MUC-1 positive versus 100% for those who were MUC-1 negative. On the other hand, the overall survival (OS) was not statistically different. In contrast, MUC-1 expression was predictive in ALK-negative patients for the 5-year PFS (26% in MUC-1-positive vs. 70.8% in MUC-1-negative patients) and OS (55.6% vs. 93.3%). Another useful marker might be survivin, a member of the inhibitor of apoptosis (IAP) family that inhibits cell

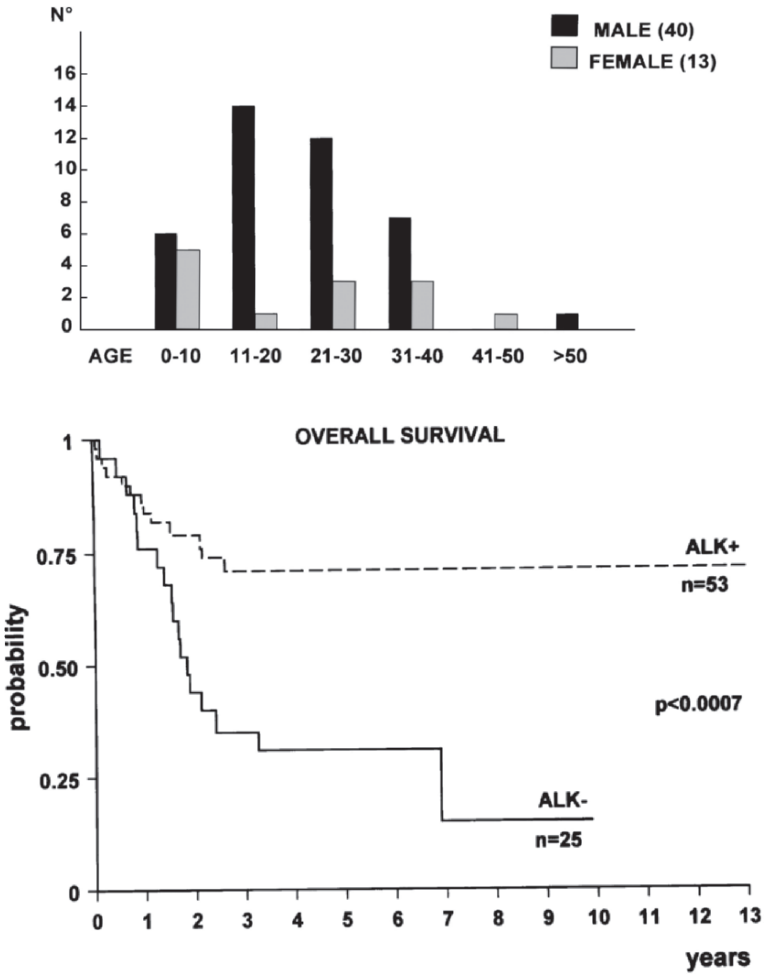

Figure 15.3 **(A)** Age distribution in primary systemic ALCL; **(B)** prognosis in primary systemic ALCL

death via inhibition of apoptotic pathways (34). In patients with ALK-positive tumors, the 5-year failure-free survival (FFS) rate was 34% for patients with survivin-positive tumors versus 100% for patients with survivin-negative tumors. The 5-year OS in ALK-positive patients was 56% for survivin-positive tumors (versus 100% for survivin-negative tumors). Accordingly, in the ALK-negative group, the 5-year OS rate was 60% for survivin-positive tumors (92% for negative tumors) and the 5-year FFS rate was 46% versus 89% for (survivin-positive vs. surviving-negative) (35).

Clinically, ALK-positive ALCL frequently presents as an aggressive stage III–IV disease, usually associated with B-symptoms (75%), especially high fever.

Extranodal involvement is frequent (60%), with ~40% of patients showing two or more extranodal sites of the disease. In a large study, the frequency of extranodal sites of lymphoma involvement was as follows: skin, 21%; bone (solitary or multiple lesions), 17%; soft tissues, 17%; lung, 11%; and liver. 8%, with involvement of the gut and central nervous system only rarely (30). The incidence of bone marrow involvement is ~30% when checked with immunohistochemistry (36). Of course, almost all patients present with disseminated lymphadenopathy, whereas about 40% have lymphadenopathy as their only clinical manifestation. The age-adjusted International Prognostic Index (IPI) is valuable in ALCL regardless of the x-ALK expression. Patients with an IPI of 0 and 1 show a 5-year OS of 94%, whereas for patients with a higher IPI, the OS is only 41%.

Thus, depending on the x-ALK protein expression and the IPI, certainly different initial treatment strategies are necessary for patients with a diagnosis of an ALCL. Whether other predictive markers as MUC-1 or survivin should be incorporated into the treatment algorithm remains unclear to date.

15.3.4.2 First-Line Therapy

The excellent outcome of low-risk ALK-positive lymphoma (age-adjusted IPI 0 and 1) justifies the use of a treatment protocol consisting of alkylating agents, anthracyclines, vinca alkaloids, and corticosteroids (i.e., cyclophosphamide, doxorubicin, vincristine, prednisone—CHOP-like regimens) as first-line therapy. It must be stated though that many other more aggressive polychemotherapy regimens have been reported [as reviewed by Jacobsen recently (37)], including so-called third-generation regimens. Unfortunately, none of them was tested in a prospectively randomized study and the limited numbers of patients and the marked heterogeneity of patient characteristics and schedules used makes it impossible to favor one of them. This situation would warrant a randomized comparison of less versus more intensive conventional polychemotherapy as induction therapy, but if the results of aggressive B-cell lymphomas can be extrapolated to ALCL, this approach is not very promising.

15.3.4.3 High-Dose Chemotherapy and Stem Cell Transplantation

An even more aggressive strategy is represented by upfront high-dose chemotherapy and autologous stem cell transplantation (APBSCT). The largest report on this strategy so far is the EBMT (European Group for Blood and Marrow Transplantation) registry analysis. In this retrospective analysis, only 1 out of 15 patients transplanted in first complete remission relapsed. In contrast, 6 of 15 patients who were transplanted in a second or higher complete remission relapsed. Accordingly, patients with a partial remission prior to transplant or refractory disease showed a much worse outcome (progressive disease in 6/18 and 14/16, respectively). Disease status at transplant, younger age, absence of B-symptoms, and lack of extranodal

disease indicated a better prognosis (38). Also, prospective trials have evaluated the use of APBSCT in the first complete remission. All of them are rather small and do not have a comparative arm or a prospectively defined control group, which makes the interpretation of the results difficult. Nevertheless, results of these trials are good for ALK-positive ALCL with an OS of around 90% (39–41). However, APBSCT is not regarded as the standard of care for patients with ALK-positive, IPI low–intermediate-risk ALCL, and the use of APBSCT in first remission warrants further prospective investigation.

For patients with high-risk ALK-positive or ALK-negative lymphoma, the situation is unclear as well and APBSCT has not been shown to improve the outcome so far. ALK-negative patients with relapsed disease are not likely to benefit from APBSCT. Thus, at least, these patients might be enrolled into clinical trials investigating new therapies different from conventional chemotherapy.

Although allogeneic stem cell transplantation has been reported to be successful in single cases, this option still is experimental and might be reserved for younger patients with refractory disease.

15.3.4.4 Experimental Approaches

Experimental approaches in clinical trials include anti-CD30 immunotherapy. Because strong CD30 overexpression is a common feature of ALCL and CD30 is, therefore, an attractive target, evaluation of this approach is ongoing for several years now. So far, two antibodies have entered clinical trials with some encouraging responses in phase I/II studies (SGN-30 and MDX-060) (see Figure 15.4). The SGN-30 antibody is currently being evaluated in an international phase II study. In addition to CD30, ALCL also often expresses the CD25 antigen (IL-2 receptor). Therefore, a recombinant fusion protein of IL-2 and diphtheria toxin (denileukin diftitox) is currently being studied in combination with CHOP in a phase II study.

Another new class of drugs are the histone deacetylase inhibitors (HDACs). HDACs regulate gene expression in a variety of cells and inappropriate deacetylation of antiproliferating genes is thought to be important in the pathogenesis of neoplasias. HDAC inhibitors can induce gene activation, cellular differentiation, cell growth arrest, and apoptosis in cancer cells by restoring the balance between

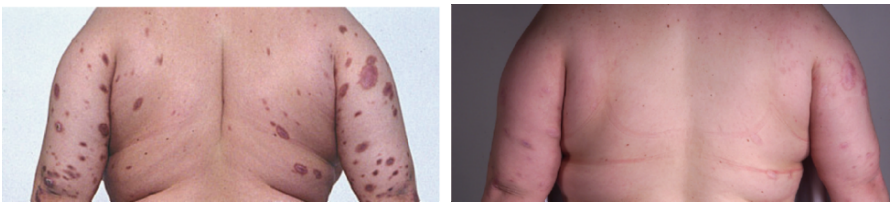

Figure 15.4 Skin lesions due to cutaneous ALCL before **(A)** and after treatment **(B)** with the anti-CD30 antibody MDX-060

the acetylation and deacetylation of genes (42). A variety of HDAC inhibitors are currently in clinical trials [including depsipeptide, SAHA (vorinostat), and PXD101] and should be taken into account for patients with relapsed or refractory ALCL.

Of course, direct targeting of the ALK-containing fusion protein in ALK-positive ALCL would be an ideal therapy. So far, only one preclinical study is available, using a fused pyrrolocarbazole-derived small molecule. This molecule showed ALK-inhibitory activity and induced apoptosis in NPM/ALK-transfected mouse embryonic fibroblasts (43).

In summary, some new therapeutic options are currently available for relapsed or refractory ALCL patients and, thus, these patients should be treated within clinical trials to further improve the knowledge about this rare disease.

15.4 Primary Cutaneous CD30-Positive T-cell Lymphoproliferative Disorders

15.4.1 Introduction

Primary cutaneous CD30-positive lymphoproliferative disorders (LPDs) account for ~30% of cutaueous T-cell lymphomas (CTCL). According to the WHO-EORTC classification system for cutaneous lymphomas, this group includes C-ALCL, LyP, and borderline cases (44). It is now generally accepted that C-ALCL and LyP form a spectrum of disease and that the histology is not sufficient to differentiate between these two ends of this spectrum. LyP, as the starting point of this spectrum, is a rather indolent chronic, recurrent, self-healing papulonecrotic or papulonodular skin disease, whereas C-ALCL is defined by its large anaplastic cells and the rapid growth of the mostly solitary or localized nodules at the end of the spectrum (44). The course of the disease and the clinical appearance must be taken into account to confirm the diagnosis (see Figure 15.5). Accordingly, the term “borderline case” should be used only in cases in which a definite distinction between C-ALCL and LyP cannot be made despite this thorough clinicopathologic correlation. The course of the disease will usually exhibit the final diagnosis (45).

15.4.2 Clinical Presentation

Lymphomatoid papulosis has been first described in 1968 as recurrent, self-healing, clinically benign disease (46). It occurs mainly in adults (median age: 45 years; male-to-female ratio: 1.5:1) and is characterized by the presence of papular, papulonecrotic, and/or nodular skin lesions at different stages of development. Lesions

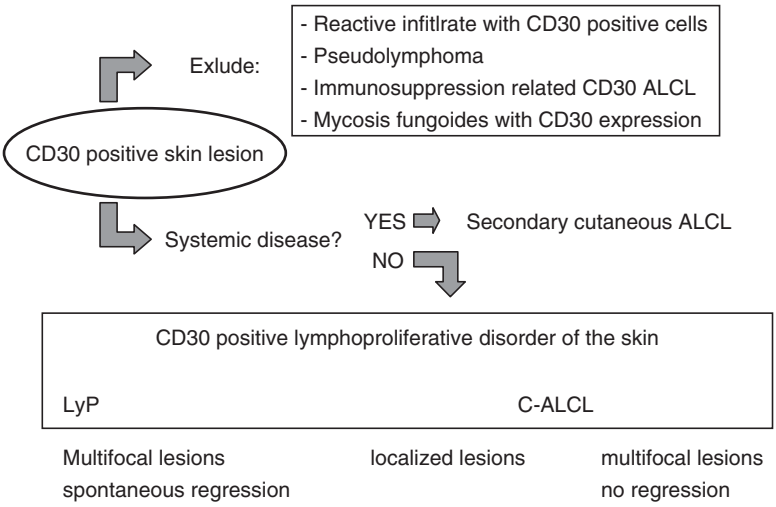

Figure 15.5 Diagnosis of LPD. (Adapted from Refs.45 and 51)

are found predominantly on the trunk and limbs and usually disappear within 3–12 weeks. Coexpression of CD30 and CD30L has been proposed to be responsible for the spontaneous regression often observed in this disease (10). It is a chronic disease that might last from some months to more than 40 years in individual patients. As outlined earlier, LyP is often (20%) associated with other lymphomas, especially HL, mycosis fungoides, or ALCL (45).

Primary cutaneous anaplastic lymphoma also affects mainly adults, with a predominance of the male gender (2–3:1). In contrast to LyP, most patients present with solitary or localized nodules or tumors, with only 20% of all patients showing multifocal lesions. The tumors, which often grow out, commonly ulcerate. Spontaneous regression, as in LyP, occurs, but not as often. After complete resection, relapses are seen frequently in the skin. Extracutaneous dissemination occurs in 10% of the patients and mainly involves the regional lymph nodes.

Importantly, the prognosis for patients with C-ALCL infiltration of regional lymph nodes is not worse than for those with cutaneous disease only. Overall survival is very good, exceeding 90% at 10 years. The prognosis for patients with LyP is even better, with only 2% disease-related mortality at ~6 years.

15.4.3 Therapy

The first choice of therapy for C-ALCL is surgical resection if the patient has only a solitary skin lesion or a few localized nodules. If resection is not possible in patients with few lesions, radiotherapy is also very effective. In cases with disseminated skin involvement, low-dose methotrexate on a weekly schedule often exhibits

good clinical results. This is also the first choice of treatment for patients with LyP, who usually present with disseminated disease. Due to the chronic indolent course of the disease, a more aggressive approach is not justified in LyP. However, treatment is indicated in patients with scarring lesions. If low- dose methotrexate cannot achieve clinical improvement, psoralene and ultraviolet A phototherapy (PUVA) or locally administered chemotherapy has been used successfully. In patients with non-carring lesions, a watch-and-wait strategy is justified.

15.4.4 Diagnosis, Histopathological, and Genetic Findings

The histology of LyP is very variable and, in part, correlates with the age of the skin lesion. Three histologic subtypes of LyP (types A, B, and C) represent a spectrum with overlapping features (45). In LyP type A lesions, scattered or small clusters of large, CD30-positive, sometimes multinucleated cells are intermingled with numerous inflammatory cells, such as histiocytes, small lymphocytes, neutrophils, and/or eosinophils. LyP type B amounts to less than 10% of the three subclasses and is characterized by an epidermotropic infiltrate of small atypical cells with cerebriform nuclei similar to that observed in mycosis fungoides. In LyP type C lesions, the large CD30-positive T-cells dominate the picture and demonstrate clusters of cells mixed with relatively few inflammatory cells. For the most common LyP subtypes A and C, immunophenotyping of the neoplastic cells shows an activated CD4-positive T-cell phenotype with variable loss of CD2, CD5, and/or CD3 and frequent expression of cytotoxic proteins (granzyme B, TIA-1, perforin) (47). Only very few cases have a CD8-positive T-cell phenotype. CD30 must be expressed by more than 75% of the malignant cells by definition. In contrast to systemic CD30-positive lymphomas, LPDs express the cutaneous lymphocyte antigen (CLA) but not the epithelial membrane antigen (EMA). Also, x-ALK proteins cannot be found in LPDs (48). CD15 is generally negative. The atypical cells with cerebriform nuclei in the LyP type B lesions stain positive for CD3 and CD4 but negative for CD8 and CD30.

With regard to its genetic features, LyP is a clonal T-cell disorder with rearranged T-cell receptor genes in ~60–70% of all lesions. In C-ALCL, almost all cases show this T-cell receptor rearrangement. In some cases of C-ALCL, polyclonal CD30-positive cells could be detected, suggesting that the malignant CD30-positive clone has emerged from this background population (49). There are no other typical genetic aberrations; especially the t(2;5)(p23;q35) is not found in LPDs in contrast to the primary systemic ALCL. Interestingly, identical rearrangements have been demonstrated in LyP lesions and associated lymphomas (50). This observation has been made for many other cases of LPD and accompanying lymphomas, including mycosis fungoides, HL, and ALCL (49) These cases suggest a common tumor stem cell harboring this rearrangement. Different and distinct lymphomas can arise from this stem cell in one patient, depending on additional genetic events caused by genetic instability.

15.4.5 Differential Diagnosis

Some LPDs express CD30 as well and therefore must be considered in the differential diagnosis. Mycosis fungoides and Sezary syndrome, which have transformed into high-grade lymphomas, might express CD30 as well as Pagetoid reticulosis, systemic T-cell lymphoma, HL, and lymphoma- and leukemia-associated cutaneous atypical T-cell reactions (51). Because CD30-positive lymphocytes can be found in reactive inflammatory disorders, these conditions might mimic LPDs (52, 53). In contrast to LyP, no waxing and waning is found in these so-called pseudolymphomas, which might be infectious or noninfectious. Typically, no clonal T-cell receptor rearrangement can be found in these lesions. All kinds of viral (e.g., herpes simplex or varicella zoster in immunocompromised patients), parasitic (e.g., scabies), and bacterial infections (e.g., tuberculosis) can be accompanied by CD30-positive lymphoid blasts (51). These observations suggest that LyP also might arise from an infection. Viruslike particles have been identified by electron microscopy in LyP lesions (54). Based on this finding, it was hypothesized that endogenous retroviral elements might be involved in the pathogenesis of LyP, although no specific virus could be detected so far.

From a practical point of view, differential diagnosis mostly involves LyP type C, C-ALCL, and mycosis fungoides in transformation. Again, the definite diagnosis cannot be made on the histopathological finding alone, but the clinical presentation must also be considered. However, patients suffering from LyP with large nodules that may last for several months before spontaneous regression might be difficult to differentiate from patients with C-ALCL. These are the so-called borderline lesions, but the term has not been included into the WHO-EORTC classification. Also, histological differentiation of primary and secondary ALCL is often impossible and additional markers as ALK or EMA must be used to distinguish these lymphomas. This differential diagnosis also depends on the staging results (see Figure 15.5). Taken together, the dermatopathologist can provide a list of differential diagnoses in most cases, but the clinical presentation must be considered to get a complete picture and to initiate the appropriate treatment for patients with CD30-positive LPDs.

References

1. Schwab U, Stein H, Gerdes J, et al. Production of a monoclonal antibody specific for Hodgkin and Sternberg-Reed cells of Hodgkin's disease and a subset of normal lymphoid cells. Nature 1982;299:65–67.
2. Durkop H, Latza U, Hummel M, et al. Molecular cloning and expression of a new member of the nerve growth factor receptor family that is characteristic for Hodgkin's disease. Cell 1992;68:421–427.
3. Stein H, Gerdes J, Schwab U, et al. Evidence for the detection of the normal counterpart of Hodgkin and Sternberg-Reed cells. Hematol Oncol 1983;1:21–29.
4. Younes A, Kadin ME. Emerging applications of the tumor necrosis factor family of ligands and receptors in cancer therapy. J Clin Oncol 2003;21:3526–3534.

5. Nagata S, Ise T, Onda M, et al. Cell membrane-specific epitopes on CD30: potentially superior targets for immunotherapy. Proc Natl Acad Sci USA 2005;102:7946–7951.
6. DeYoung AL, Duramad O, Winoto A. The TNF receptor family member CD30 is not essential for negative selection. J Immunol 2000;165:6170–6173.
7. Podack ER, Strbo N, Sotosec V, et al. CD30-governor of memory T cells? Ann NY Acad Sci 2002;975:101–113.
8. Florido M, Borges M, Yagita H, et al. Contribution of CD30/CD153 but not of CD27/CD70, CD134/OX40L, or CD137/4-1BBL to the optimal induction of protective immunity to *Mycobacterium avium*. J Leukoc Biol 2004;76:1039–1046.
9. Al-Shamkhani A. The role of CD30 in the pathogenesis of haematopoietic malignancies. Curr Opin Pharmacol 2004;4:355–359.
10. Mori M, Manuelli C, Pimpinelli N, et al. CD30-CD30 ligand interaction in primary cutaneous CD30(+) T-cell lymphomas: a clue to the pathophysiology of clinical regression. Blood 1999;94:3077–3083.
11. Stein H, Mason DY, Gerdes J, et al. The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. Blood 1985;66:848–858.
12. Stein H, Foss HD, Durkop H, et al. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood 2000;96:3681–3695.
13. Benharroch D, Meguerian-Bedoyan Z, Lamant L, et al. ALK-positive lymphoma: a single disease with a broad spectrum of morphology. Blood 1998;91:2076–2084.
14. Falini B, Bigerna B, Fizzotti M, et al. ALK expression defines a distinct group of T/null lymphomas ("ALK lymphomas") with a wide morphological spectrum. Am J Pathol 1998;153:875–886.
15. Pulford K, Lamant L, Morris SW, et al. Detection of anaplastic lymphoma kinase (ALK) and nucleolar protein nucleophosmin (NPM)-ALK proteins in normal and neoplastic cells with the monoclonal antibody ALK1. Blood 1997;89:1394–1404.
16. Chan JK, Buchanan R, Fletcher CD. Sarcomatoid variant of anaplastic large-cell Ki-1 lymphoma. Am J Surg Pathol 1990;14:983–988.
17. Kinney MC, Collins RD, Greer JP, et al. A small-cell-predominant variant of primary Ki-1 (CD30)+ T-cell lymphoma. Am J Surg Pathol 1993;17:859–868.
18. Le Beau MM, Bitter MA, Larson RA, et al. The t(2;5)(p23;q35): a recurring chromosomal abnormality in Ki-1-positive anaplastic large cell lymphoma. Leukemia 1989;3:866–870.
19. Kaneko Y, Frizzera G, Edamura S, et al. A novel translocation, t(2;5)(p23;q35), in childhood phagocytic large T-cell lymphoma mimicking malignant histiocytosis. Blood 1989;73:806–813.
20. Rimokh R, Magaud JP, Berger F, et al. A translocation involving a specific breakpoint (q35) on chromosome 5 is characteristic of anaplastic large cell lymphoma ('Ki-1 lymphoma'). Br J Haematol 1989;71:31–36.
21. Mason DY, Bastard C, Rimokh R, et al. CD30-positive large cell lymphomas ('Ki-1 lymphoma') are associated with a chromosomal translocation involving 5q35. Br J Haematol 1990;74:161–168.
22. Bischof D, Pulford K, Mason DY, et al. Role of the nucleophosmin (NPM) portion of the non-Hodgkin's lymphoma-associated NPM-anaplastic lymphoma kinase fusion protein in oncogenesis. Mol Cell Biol 1997;17:2312–2325.
23. Kutok JL, Aster JC. Molecular biology of anaplastic lymphoma kinase-positive anaplastic large-cell lymphoma. J Clin Oncol 2002;20:3691–3702.
24. Marzec M, Kasprzycka M, Liu X, et al. Oncogenic tyrosine kinase NPM/ALK induces activation of the rapamycin-sensitive mTOR signaling pathway. Oncogene 2007. Aug 23; 26(38), 5606–5614.
25. Kuefer MU, Look AT, Pulford K, et al. Retrovirus-mediated gene transfer of NPM-ALK causes lymphoid malignancy in mice. Blood 1997;90:2901–2910.
26. Trumper L, Pfreundschuh M, Bonin FV, et al. Detection of the t(2;5)-associated NPM/ALK fusion cDNA in peripheral blood cells of healthy individuals. Br J Haematol 1998;103:1138–1144.

27. Armstrong F, Duplantier MM, Trempat P, et al. Differential effects of X-ALK fusion proteins on proliferation, transformation, and invasion properties of NIH3T3 cells. Oncogene 2004;23:6071–6082.
28. Mir SS, Richter BW, Duckett CS. Differential effects of CD30 activation in anaplastic large cell lymphoma and Hodgkin disease cells. Blood 2000;96:4307–4312.
29. Krysov SV, Rowley TF, Al-Shamkhani A. Inhibition of p38 mitogen-activated protein kinase unmasks a CD30-triggered apoptotic pathway in anaplastic large cell lymphoma cells. Mol Cancer Ther 2007;6:703–711.
30. Falini B. Anaplastic large cell lymphoma: pathological, molecular and clinical features. Br J Haematol 2001;114:741–760.
31. Gascoyne RD, Aoun P, Wu D, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. Blood 1999;93:3913–3921.
32. Shiota M, Nakamura S, Ichinohasama R, A. et al. Anaplastic large cell lymphomas expressing the novel chimeric protein p80NPM/ALK: a distinct clinicopathologic entity. Blood 1995;86:1954–1960.
33. Rassidakis GZ, Goy A, Medeiros LJ, et al. Prognostic significance of MUC-1 expression in systemic anaplastic large cell lymphoma. Clin Cancer Res 2003;9:2213–2220.
34. Altieri DC. Validating survivin as a cancer therapeutic target. Nat Rev Cancer 2003;3:46–54.
35. Schlette EJ, Medeiros LJ, Goy A, et al. Survivin expression predicts poorer prognosis in anaplastic large-cell lymphoma. J Clin Oncol 2004;22:1682–1688.
36. Fraga M, Brousset P, Schlaifer D, et al. Bone marrow involvement in anaplastic large cell lymphoma. Immunohistochemical detection of minimal disease and its prognostic significance. Am J Clin Pathol 1995;103:82–89.
37. Jacobsen E. Anaplastic large-cell lymphoma, T-/null-cell type. Oncologist 2006;11:831–840.
38. Fanin R, Ruiz de Elvira MC, Sperotto A, et al. Autologous stem cell transplantation for T and null cell CD30-positive anaplastic large cell lymphoma: analysis of 64 adult and paediatric cases reported to the European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant 1999;23:437–442.
39. Fanin R, Silvestri F, Geromin A, et al. Primary systemic CD30 (Ki-1)-positive anaplastic large cell lymphoma of the adult: sequential intensive treatment with the F-MACHOP regimen (+/– radiotherapy) and autologous bone marrow transplantation. Blood 1996;87:1243–1248.
40. Fanin R, Sperotto A, Silvestri F, et al. The therapy of primary adult systemic CD30-positive anaplastic large cell lymphoma: results of 40 cases treated in a single center. Leuk Lymphoma 1999;35:159–169.
41. Deconinck E, Lamy T, Foussard C, et al. Autologous stem cell transplantation for anaplastic large-cell lymphomas: results of a prospective trial. Br J Haematol 2000;109:736–742.
42. Marks P, Rifkind RA, Richon VM, et al. Histone deacetylases and cancer: causes and therapies. Nat Rev Cancer 2001;1:194–202.
43. Wan W, Albom MS, Lu L, et al. Anaplastic lymphoma kinase activity is essential for the proliferation and survival of anaplastic large-cell lymphoma cells. Blood 2006;107:1617–1623.
44. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768–3785.
45. Bekkenk MW, Geelen FA, van Voorst Vader PC, et al. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Blood 2000;95:3653–3661.
46. Macaulay WL. Lymphomatoid papulosis. A continuing self-healing eruption, clinically benign–histologically malignant. Arch Dermatol 1968;97:23–30.
47. Kaudewitz P, Stein H, Dallenbach F, et al. Primary and secondary cutaneous Ki-1+ (CD30+) anaplastic large cell lymphomas. Morphologic, immunohistologic, and clinical-characteristics. Am J Pathol 1989;135:359–367.
48. DeCoteau JF, Butmarc JR, Kinney MC, et al. The t(2;5) chromosomal translocation is not a common feature of primary cutaneous CD30+ lymphoproliferative disorders: comparison with anaplastic large-cell lymphoma of nodal origin. Blood 1996;87:3437–3441.

49. Kadin ME. Pathobiology of CD30+ cutaneous T-cell lymphomas. J Cutan Pathol 2006;33 (Suppl 1):10–17.
50. Davis TH, Morton CC, Miller-Cassman R, et al. Hodgkin's disease, lymphomatoid papulosis, and cutaneous T-cell lymphoma derived from a common T-cell clone. N Engl J Med 1992;326:1115–1122.
51. Kempf W. CD30+ lymphoproliferative disorders: histopathology, differential diagnosis, new variants, and simulators. J Cutan Pathol 2006;33(Suppl 1):58–70.
52. Durkop H, Foss HD, Eitelbach F, et al. Expression of the CD30 antigen in non-lymphoid tissues and cells. J Pathol 2000;190:613–618.
53. Cepeda LT, Pieretti M, Chapman SF, et al. CD30-positive atypical lymphoid cells in common non-neoplastic cutaneous infiltrates rich in neutrophils and eosinophils. Am J Surg Pathol 2003;27:912–918.
54. Kempf W, Kadin ME, Dvorak AM, et al. Endogenous retroviral elements, but not exogenous retroviruses, are detected in CD30-positive lymphoproliferative disorders of the skin. Carcinogenesis 2003;24:301–306.
55. Foss HD, Anagnostopoulos I, Araujo I, et al. Anaplastic large-cell lymphomas of T-cell and null-cell phenotype express cytotoxic molecules. Blood 1996;88:4005–4011.