5 Primary Cutaneous and Systemic CD30+ T-cell Lymphoproliferative Disorders

Marshall E. Kadin and Francine Foss

Historical Perspective and Overview

CD30+ lymphoproliferative diseases are a recently recognized group of diseases whose identification was made possible by reaction of the tumor cells with an antibody raised against a Hodgkin lymphoma cell line, L428 [1]. In screening reactivity of the antibody, Stein and coworkers discovered a subset of large-cell lymphomas which also expressed the Hodgkin-associated antigen [2]. The antibody was called Ki-1 after the location of investigators in Kiel, Germany, but later was given the cluster designation CD30. CD30 was found to be a member of the TNF receptor superfamily [3]. Mir and coworkers showed a dual effect of CD30 signaling, causing proliferation of Hodgkin cells but apoptosis of anaplastic large-cell lymphoma (ALCL) cells [4]. In 1985, Kadin and coworkers observed that the atypical Reed–Sternberg-like cells in lymphomatoid papulosis (LyP), a recurrent cutaneous eruption, express CD30 as well as T-cell antigens [5]. This led to clarification of the histogenesis of a spectrum of cutaneous papules, nodules, and tumors, initially thought to be regressing atypical histiocytosis, and later to become known as CD30+ cutaneous lymphoproliferative disorders. This spectrum includes LyP, cutaneous ALCL, and borderline lesions which are not readily be distinguished clinically or histologically from LyP or ALCL. In 1986, Kadin and coworkers described a series of children and adolescents with skin lesions and peripheral lymphadenopathy [6]. Unlike patients with CD30+ cutaneous lymphoproliferative disorders who lack lymphadenopathy, these children with lymphadenopathy at presentation had an aggressive disease requiring multiagent chemotherapy. This clinicopathologic entity became known as systemic ALCL. Rimokh et al. found that cell line Karpas 299 derived from a pleural effusion of a patient with systemic ALCL contained a reciprocal translocation t(2;5)(p23;q35) [7]. Further studies revealed this is a recurrent translocation characteristic of 80% of systemic ALCL [8]. In 1994, Morris et al. cloned the t(2;5) breakpoint and discovered a novel oncogenic protein derived from fusion of nuclear chaperone protein, nucleophosmin (NPM) at chr. 5p35, and a newly recognized tyrosine kinase designated as ALK after Anaplastic Lymphoma Kinase, at 2p23 [9]. Japanese investigators raised a polyclonal antibody against the p80 component of ALK which revealed that ALK positive (ALK+) ALCL has a better prognosis than ALK(−) ALCL [10]. Pulford et al. found ALK to be immunogenic and

M.E. Kadin
Department of Dermatology and Skin Surgery,
Boston University of Medicine and Roger
Williams Medical Center,
Providence, RI, USA

F. Foss (✉)
Department of Medical Oncology/Hematology,
Yale University School of Medicine,
333 Cedar Street, FMP 130, PO Box 208032,
New Haven, CT 06520, USA
e-mail: Francine.foss@yale.edu

F. Foss (ed.), *T-Cell Lymphomas*, Contemporary Hematology,
DOI 10.1007/978-1-62703-170-7_5, © Springer Science+Business Media New York 2013

raised a monoclonal antibody (ALK-1) which now is used clinically to aid identification and diagnosis of systemic ALCL [11]. Clinical studies later confirmed that ALK+ systemic ALCL is a clinicopathologic entity occurring mainly in children and adolescents with a significantly better prognosis than ALK(−) systemic ALCL or peripheral T-cell lymphoma, not otherwise specified [12].

Cutaneous CD30+ Lymphoproliferative Disorders

Primary cutaneous CD30+ T-cell lymphoproliferative disorders are the second most common type of cutaneous T-cell lymphomas (CTCL). These disorders comprise a spectrum of clinically benign LyP and primary cutaneous anaplastic large-cell lymphoma (PCALCL). The peak incidence is in the fifth decade for LyP and sixth decade for PCACL, but children are also affected. Both LyP and PCALCL have an excellent prognosis. However, LyP is associated with development of malignant lymphoma (mycosis fungoides, Hodgkin lymphoma, or ALCL) in 20% of cases, and also with an increased risk of non-lymphoid cancers. The diagnosis of LyP is difficult and often delayed. PCALCL must be distinguished from secondary skin lesions in systemic ALCL which confer a poor prognosis. Correlation of clinical findings with histopathology and immunopathology (stains for ALK kinase, epithelial membrane antigen (EMA), and cutaneous lymphocyte antigen (CLA)) is important to achieve a correct diagnosis. When a diagnosis of CD30+ PCLPD is established, minimal clinical staging is required. Bone marrow involvement is rare and thus bone marrow biopsy is not indicated. Lymph node involvement is uncommon and when it occurs does not appear to portend a poor prognosis. Low-dose methotrexate (10–25 mg weekly) is the most effective therapy for primary cutaneous lymphoproliferative disorders but is usually reserved only for aggressive cases of LyP and multifocal lesions of cutaneous ALCL. Many patients with LyP can be followed expectantly with special attention to change in character of skin lesions or development of lymphadenopathy. Patients with localized cutaneous ALCL can be treated with irradiation. Extracutaneous spread of disease is an indication for multiagent chemotherapy. Other treatment alternatives are discussed.

Cutaneous CD30+ Lymphoproliferative Disorders

The primary cutaneous CD30-positive (CD30+) T-cell lymphoproliferative disorders are a group of largely indolent diseases that manifest as nodules or tumors of the skin. The European Organization for Research and Treatment of Cancer has developed a modification of the World Health Organization lymphoma classification system that specifically categorizes these entities. According to Willemze et al., the CD30+ diseases include primary ALCL, primary CD30+ lymphoproliferative disorder, and LyP [13]. These comprise about 25% of the CTCL. Often confused with more aggressive T-cell lymphomas with similar histopathologic features, these diseases are difficult to diagnose and poorly understood (Fig. 5.1). LyP patients have clinically benign self-healing skin papules and/or nodules which have the unexpected histopathology of a high-grade malignant lymphoma [14]. Primary cutaneous ALCL also have the histology of a high-grade lymphoma but only 25% of lesions regress spontaneously. Because of their histologic appearance and frequent recurrence, patients with CD30+ PCLPD may be treated unnecessarily with multiagent chemotherapy. However, the prognosis is excellent. Disease-specific survival of LyP patients at 5 years is 100% and overall survival at 5 years is 92% [15, 16]. Disease-specific survival of PCALCL is 85–90% [15, 16].

Diagnosis

LyP often is not diagnosed correctly upon presentation; it is common for symptoms to persist for 1–3 years before a correct diagnosis is established. A variety of diagnoses are entertained but most commonly insect, spider, or mosquito bite.

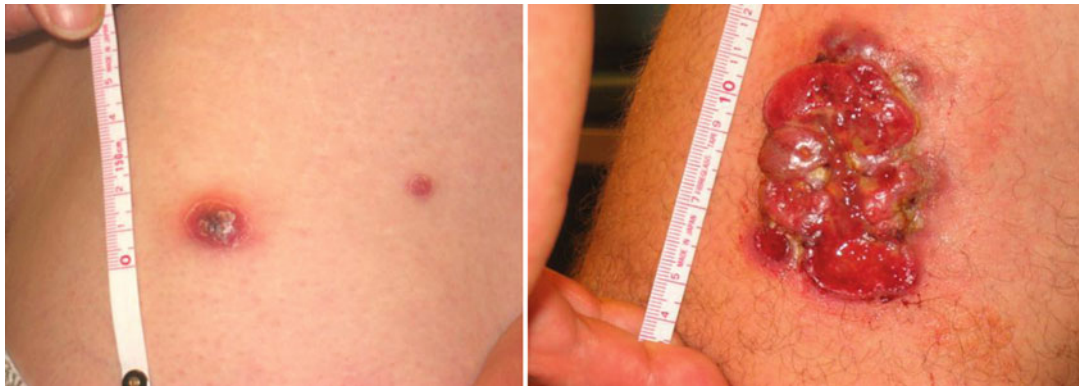

Fig. 5.1 Spectrum of LyP and Cutaneous ALCL in an individual patient. *Left*: Two LyP lesions are seen with erythema and central necrosis in the larger lesion. *Right*: The cutaneous ALCL is larger and elevated without signs of regression

This is likely due to the common occurrence of bites with associated erythema and central necrosis, whereas most patients and many clinicians are unfamiliar with LyP.

Tumor cells in both LyP and PCALCL are derived from activated T-cells which express CD30 antigen. The CD30+ cells are larger than normal lymphocytes and have basophilic cytoplasm and large nuclei with a prominent nucleolus resembling immunoblasts. These cells often are bi- or multinucleated giving the appearance of Reed–Sternberg cells. Mitoses are frequent and often atypical. In LyP, tumor cells are scattered throughout the upper dermis and surrounded by small lymphocytes, neutrophils, and eosinophils. In PCALCL, tumor cells form large clusters or sheets that generally extend from the dermal–epidermal junction down into the subcutaneous fatty tissue. Thus the distinction of LyP from ALCL largely depends on the density of CD30+ tumor cells and the extent of dermal and subcutaneous involvement.

Differential Diagnosis

The frequency of LyP in male children poses an interesting differential diagnosis with pityriasis lichenoides et varioliformis acuta (PLEVA). PLEVA can present with similar cutaneous lesions but has a different prognostic significance. In particular, there is no increased risk to develop lymphoma among patients with PLEVA while the risk of lymphoma in LyP patients approaches 20% [15, 17]. PLEVA is more common in children and young adults than in older patients so the most difficult differential diagnosis is in the age group under 30 years. Skin lesions in PLEVA tend to be hemorrhagic papules whereas LyP lesions vary from papules to small nodules often with central whitening and ulceration due to accumulation of neutrophils in the epidermis. LyP shows more frequent large bizarre cells including bi- or multinucleated cells with basophilic cytoplasm; these cells are CD30+. Such cells are infrequent or absent in PLEVA. Necrosis of individual keratinocytes (Civatte and colloid bodies) is usual in PLEVA but absent in LyP. Further, immunopathology reveals a predominance of CD4+ lymphocytes in LyP but mostly CD8+ lymphocytes in PLEVA. Nodular scabies is also in the differential diagnosis of LyP, particularly in children. Scabies also includes CD30+ cells. It is found in the inguinal and genital areas which can be affected in LyP. In scabies, the CD30+ cells co-express B-cell antigens whereas CD30+ cells in LyP express T-cell antigens.

Distinction from Systemic ALCL

Oncologists need to be aware of the distinction of CD30+ PCLPD from secondary skin lesions in patients with nodal/systemic ALCL. Skin is the

most common extranodal site of disease in nodal/systemic ALCL and skin lesions confer an increased risk of failure in childhood ALCL [18, 19]. When skin lesions are a presenting manifestation of nodal/systemic ALCL, the distinction from CD30+ PCLPC is imperative. The distinction of skin lesions in systemic ALCL from CD30+ PCLPC can be difficult on purely clinical grounds and may be difficult as well to achieve by routine histopathology. One of the most helpful approaches is to test the tumor cells for expression of the ALK protein. This is expressed in skin lesions of most patients with nodal/systemic ALCL but not in the large majority of patients with CD30+ PCLPD. Rare exceptions occur and in such cases, therefore a panel of immunologic markers is recommended. EMA is expressed on tumor cells in 82% of nodal/systemic ALCL but <5% of CD30+ PCLPD [20]. CLA also is more frequently expressed in CD30+ PCLPD (44%) than on tumor cells in nodal/systemic ALCL (18%). Thus, a successful immunopathologic distinction of CD30+ PCLPD from nodal/systemic ALCL can be made in most cases.

Staging of Cutaneous CD30+ Lymphoproliferative Disorders

When a diagnosis of CD30+ PCLPD is established, minimal clinical staging is required. Bone marrow involvement is rare and thus bone marrow biopsy is not indicated. Lymph node involvement is uncommon and when it occurs does not appear to portend a poor prognosis [15]. In the case of systemic involvement, regional lymph nodes are the most common sites of involvement. Often this is minimal microscopic involvement with tumor cells confined to lymph node sinuses and not effacing lymph node architecture. This may be detected by immunohistochemical staining for CD30, which in combination with morphology, can reveal microscopic disease.

Etiology

Although CD30+ PCLPD are rare, all races, ages, and both genders are affected. The prevalence of CD30+ CLPD in the USA is unknown but an LyP patient support group includes 850 members indicating a prevalence approaching 3 per million. Most European studies show a male predominance whereas our US registry has a nearly equal number of males and females. The peak age incidence of LyP appears to be in the fifth decade. However, children are also affected. Primary cutaneous ALCL has a peak incidence after age 50 but can also affect children and young adults.

CD30 signaling is known to have an effect on the growth and survival of lymphoid cells. CD30 transcription is under control of a genetically determined polymorphic promoter. Franchina et al. analyzed CD30 promoter microsatellite alleles in 32 unrelated Caucasian patients diagnosed with LyP alone or LyP plus lymphoma, as well as 8 unrelated Caucasian patients with CD30+ primary cutaneous ALCL [21]. Controls were 57 Caucasian healthy volunteers and patients with non-lymphoid malignancies. Patients and controls were gender-matched. We determined that two allelic forms of the CD30 promoter microsatellite repressive element, designated 30M377 and 30M362, are associated with the development of LyP and CD30+ lymphomas in LyP patients, respectively. These findings suggest that allele-specific differences in the control of CD30 transcription may determine the pathogenesis of the spectrum of CD30+ cutaneous lymphoproliferative disorders.

Njisten et al. reported 35 cases of LyP beginning in childhood [22]. These patients had a significantly higher prevalence of atopy (RR3.1, 95%CI). Compared with the general population, patients with childhood-onset LyP had a significantly increased risk of developing non-Hodgkin lymphoma (relative risk, 226.2; 95% confidence interval, 73.4–697.0). Fletcher also reported an association of CD30+ CLPD with atopic eczema beginning in childhood [23]. Three patients had primary cutaneous ALCL, of whom two developed systemic disease and one died. The fourth patient developed LyP type A which resolved after withdrawal of cyclosporine therapy. We concluded that LyP presents similarly in children and adults, including the risk to develop lymphoma, and patients should be closely

monitored for development of lymphoma throughout their lives.

A major concern of LyP patients, and parents of children with LyP, is whether the affected individual will develop a malignant lymphoma. There are many reported individual or small series of cases, but few reports of large numbers of affected patients. In one series, including a review of the literature, 50 patients with LyP-associated lymphomas were evaluated [24]. Three main types of LyP-associated lymphomas were distinguished: cases associated with mycosis fungoides (19/50), Hodgkin's disease (12/50), and CD30+ large-cell lymphoma (16/50). Mycosis fungoides and Hodgkin's disease could develop before, after, or concurrent with LyP, but CD30+ large-cell lymphoma always developed in patients with existing LyP, often showing a slow progression from regressing LyP lesions to persistent skin tumors. Patients with mycosis fungoides, Hodgkin's disease, and CD30+ large-cell lymphoma limited to the skin generally had a favorable prognosis. The prognosis of patients developing a systemic CD30+ large-cell lymphoma was generally poor. Some LyP patients develop Hodgkin's disease followed by a systemic CD30+ large-cell lymphoma which also is associated with a poor prognosis. In a subsequent review of 118 LyP patients in the Netherlands, 23 (19%) developed malignant lymphoma, 11 developed mycosis fungoides, 10 CD30+ LCL, and 2 Hodgkin lymphoma [15].

The relationship between LyP, a T-cell disorder, and Hodgkin's disease, primarily a B-cell disorder, is poorly understood. I am aware of patients who had LyP lesions before or after Hodgkin's disease. When the Hodgkin's disease was treated with chemotherapy, the LyP lesions often disappeared but temporarily only to reappear shortly thereafter. In rare cases, a clonal relationship between the CD30+ cells in LyP and Hodgkin's disease was shown by DNA sequencing. A clonal relationship between LyP and mycosis fungoides, and ALCL is firmly established [25, 26].

In a case–control study of 57 patients with biopsy-proven LyP and 67 individually matched controls, there was a significant increased frequency of prior or coexisting lymphoproliferative disorders, an increased frequency of non-lymphoid malignancies, and exposure to radiation therapy [27]. Among patients with LyP, three had a history of Hodgkins disease, three had NHL, and ten had mycosis fungoides; none of the control subjects reported such histories. Prospective study of this group of patients over an 8-year period (1988–1996) revealed that six LyP patients (10.5%) and one control (1.5%) developed non-lymphoid malignancies. Two patients and one controls developed lymphoid malignancies. The expected numbers of non-lymphoid and lymphoid malignancies in the LyP group based on SEER data were 1.93 and 0.15 respectively, yielding a relative risk (with 95% CI) of 3.11 (1.26–6.47) for non-lymphoid malignancies and 13.33 (2.44–44.05) for malignant lymphoma in LyP patients. There was no significant difference between observed and expected numbers of malignancies in the control group. These results confirm that LyP patients are at increased risk to develop lymphoid malignancies but for the first time revealed that they also have an increased risk of non-lymphoid malignancies [27].

The prognosis of LyP patients developing a systemic CD30+ large-cell lymphoma is generally poor. In two such cases, progression of LyP to systemic ALCL was associated with mutations of receptors for the lymphocyte growth inhibitor, transforming growth-factor beta, allowing unregulated growth of the CD30+ cells [28].

Treatment

Control of LyP lesions does not appear to affect the risk to develop lymphoma. Most patients with few or infrequent papules do not require therapy. For patients with extensive papules, nodules, and/or scarring lesions, particularly on the face or hands, or legs, which appear cosmetically disturbing, the most effective therapies are low-dose oral methotrexate or PUVA/UVB. Methotrexate is effective in controlling lesions in approximately 90% of patients and it induces a permanent remission in up to 20% of patients [29]. Vonderheid treated 45 patients with relatively severe LyP, CD30+ CALCL, and interface/borderline lesions with oral methotrexate. During induction, patients received 10–60 mg/week

(median 20 mg/week). Clinical improvement usually occurred quickly, typically at doses of 15–20 mg weekly, and satisfactory long-term control was achieved in 39 patients (87%) with maintenance doses given at 10–14-day intervals (range 7–28 days). Responding patients were usually free of active lesions within 4 weeks of receiving the first dose. After methotrexate was discontinued, ten patients remain free of CD30+ lesions for more than 24 months to more than 227 months (median, more than 127 months). The median total duration of methotrexate therapy for all patients exceeded 39 months (range 2–205 months). Adverse effects were generally mild and transient, and included fatigue (47%), nausea (22%), weight loss (13%), diarrhea, or gastrointestinal cramping (10%), increased serum hepatic transaminase levels (27%), anemia (11%), or leukopenia (9%). Early hepatic fibrosis was found in five of ten patients, all of whom had been treated for more than 3 years (range 38–111 months).

The mechanisms of effectiveness of methotrexate in controlling CD30+ CLPD appear to be its inhibitory effect on DNA synthesis, its anti-inflammatory effects, or both. Because the atypical lymphocytes of LyP and related CD30+ CLPD are characterized by high mitotic activity, it is likely that methotrexate inhibits cell proliferation, particularly in the early phase of lesion development. The observation that long-lasting complete remissions occur after relatively short courses (2–5 months) of methotrexate in some patients raises the possibility that high-dose methotrexate therapy, possibly combined with leucovorin (folinic acid) rescue, might provide more than suppressive therapy for some patients. Moreover, low doses of methotrexate appear to have anti-inflammatory effects separate from its anti-proliferative effect. This may explain why LyP may improve with other drugs that have anti-inflammatory effects, including corticosteroids, tetracycline, and retinoids.

In patients who do not respond to MTX, photo(chemo)-therapy should be considered. Although conventional ultraviolet phototherapy (UVB) may be effective, PUVA administered at dosages ranging from 50–480 J/cm twice weekly result in complete clearing or improvement of lesions in most patients.

Alternative Therapies

Although topically administered steroids may be useful in controlling symptoms of LyP (e.g., pruritus), steroid therapy has not been proven to control disease progression or induce remission. Similarly, antibiotic therapy has not been shown to alter the course of LyP, although anecdotally tetracycline has benefited few patients. In such patients, the role of tetracycline may be related to its anti-inflammatory effect rather its antimicrobial effects. In children with symptomatic LyP, a prolonged trial of tetracycline therapy may be used initially, particularly if there are concerns regarding side effects from MTX, photo(chemo) therapy, or other therapies. Nevertheless, neither steroid nor antibiotic therapy can be recommended as routine LyP management.

Interferon α and interferon γ therapy has been used successfully to treat LyP in few patients. The rationale for the use of interferon was provided by Japanese investigators who showed that CD30+ cells in LyP and cutaneous lymphoma have features of Th2 cells, and that skin lesions could be suppressed by local and intravenous injection of IFNα a Th1 cytokine [30]. Austrian dermatologists treated five patients with Interferon alpha subcutaneously three times per week and compared them with a group of six patients receiving photochemotherapy, antibiotics, topical corticosteroids, or surgery in an open trial. Four patients in the IFN group showed a complete remission and one a partial remission within 6 weeks. Two patients developed recurrent disease after discontinuation of short-term IFN therapy (5–7 months), and one patient remained in partial remission. In the control group, one patient went into spontaneous remission, two patients had partial remission of which one developed progressive disease; three patients had recurrent disease despite treatment. Although IFNα can alter the clinical course, it does not induce stable remissions after short-term treatment [31].

Retinoids can induce apoptosis of T-cells. M.D. Anderson investigators reported the use of bexarotene, (Targretin), a rexinoid with selectivity for intracellular retinoid X receptors in treating LyP. Ten patients with chronic and symptomatic LyP were treated prospectively with bexarotene, three orally, and seven with topical gel formulations. A favorable response with decreased numbers or duration of lesions was seen in all patients with objective responses in eight patients [32]. In patients with localized skin disease, oral bexarotene had a 54% overall response rate at an optimal dose of 300 mg/m^2/day (approximately 10 mg/kg). Topical bexarotene 1.0% gel was effective in producing remissions of individual lesions with an overall response rate of 68%.

Other topical agents that have been used historically for treatment of LyP include mechlorethamine or carmustine. There is no role for multiagent systemic chemotherapies in LyP because LyP recurs quickly and predictably in affected patients who have received such treatments [33].

Primary Cutaneous Anaplastic Large-Cell Lymphoma

While spontaneous regression is characteristic of LyP, 25% of primary cutaneous ALCL lesions will regress [26]. This number is sufficiently high to warrant as initial management expectant follow-up for a period of 4–6 weeks. If spontaneous regression occurs, therapy is not indicated, and such patients should be observed from possible disease recurrence. A small number of patients whose disease spontaneously regresses will not have recurrence of their disease. Therefore, observation for spontaneous regression is an appropriate first step in managing this disease [34].

Unfortunately, most patients with primary cutaneous ALCL have disease that does not regress spontaneously [35]. For these patients, choice of therapy depends on disease distribution and whether the lesions are singular or multiple. An exception to this approach may arise when other associated lymphoproliferative disorders such as mycosis fungoides or symptomatic LyP are simultaneously encountered, in which cases the therapeutic approach should be directed against both diseases [25].

Solitary lesions respond to local radiotherapy [34, 36]. Although surgical excision represents an alternative approach, excision specimens may contain margins involved by disease. For this reason, radiotherapy is the preferred treatment for solitary lesions. Radiotherapy consists of electron beam irradiation (4–10 million eV) with a total radiation dose of 40 Gy. Because electron beam therapy penetrates only to the dermis, there are no systemic effects, although side effects include alopecia, atrophy of sweat glands and skin, radio-dermatitis, and edema.

In general, radiotherapy is impractical for patients with multiple non-regressing lesions, although total skin electron beam therapy may be a consideration if other diseases, like mycosis fungoides, are present. For this reason, systemic therapy is the treatment of choice for this group of patients [37]. Because long-term remissions are generally not achieved with multiagent chemotherapy, less toxic, single-agent therapies are preferred. As in LyP, methotrexate can be effective in inducing remissions, but higher weekly doses of methotrexate may be necessary [29]. In affected patients whose disease is refractory or progressive on methotrexate, oral etoposide has been shown to be safe and effective therapy for primary cutaneous ALCL [38]. Other potential therapies are purine nucleoside analogs (e.g., Pentostatin), retinoids, interferon-α, and interleukin-12 [33]. Recently, studies with humanized anti-CD30 antibody have demonstrated efficacy in patients with cutaneous and systemic ALCL.

Finally, it is important to monitor patients for potential dissemination of primary cutaneous ALCL to lymph nodes and systemic organs, as well as development of associated malignancies, particularly mycosis fungoides, Hodgkin lymphoma, and B-cell non-Hodgkin lymphoma. Patients who develop systemic ALCL should be considered for multiagent systemic chemotherapies similar to those used in treatment of systemic ALCL, e.g., cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens [34, 36]. High-dose chemotherapy

followed by stem cell rescue may be indicated in affected patients who are at high risk [34, 36]. Determination of high risk may be based on prognostic factors for survival in the international prognostic index (IPI).

Approach to Patients with CD30+ PCLPD

Patients are often frustrated because of the delay in establishing the correct diagnosis. They are also fearful of their prognosis because of the association of LyP with development of other lymphomas and the high-grade histology of their lesions. The first goal is to reassure the patient about his/her favorable prognosis and to answer their questions about their disease. If the lesions scar or interfere with normal activity, therapies such as low-dose methotrexate may be effective but are not indicated for women of child-bearing age who expect to become pregnant, people with a history of liver disease, or blood dyscrasias. Other options include PUVA/UVB and topical treatments. Careful monitoring is necessary due to the increased risk of mycosis fungoides and ALCL in these patients. For patients with suspected PCALCL, clinical evaluation and pathologic studies should be done to exclude nodal/systemic ALCL. Local irradiation of skin tumors is effective, and use of methotrexate for multifocal cutaneous lesions is often successful. Follow-up of skin lesions should be carried out by a dermatologist and consultation by an oncologist when additional irradiation or multiagent chemotherapy is needed.

Systemic Anaplastic Large-Cell Lymphoma

Systemic ALCL comprises 2–3% of all NHLs [39]. The median age for ALK+ ALCL is 35 (male to female ratio: 3.0), while ALK-negative (ALK−) ALCL is 58–61 years with a male to female ratio of 0.9 [40]. Most patients (60%) have extensive disease at presentation [12, 40]. Extranodal sites in ALK− ALCL include bone, subcutaneous tissue, bone marrow, and spleen, while in ALK+ patients, the most common sites are skin, lung, liver, bone, and bone marrow. Blood involvement is rare except in children. More recently, there has been an association between ALCL and breast implants. A number of cases have reported serosal involvement in the implant pocket. De Jong et al. reported an odds ratio of 18.2 (95% confidence interval, 2.1–156.8) for ALCL associated with breast prostheses [41].

NPM-ALK expression in ALCL has been shown to be a significant prognostic factor [10], with 5-year OS of 93% vs. 37% ($P<0.00001$) and 5-year FFS of 88% vs. 37% ($P<0.0001$) [42]. A retrospective review by Savage et al. confirmed the superior survival of systemic ALK+ ALCL compared with ALK− cases (5-year FFS 60% vs. 36%; $P=0.015$; and 5-year OS 70% vs. 49%; $P=0.016$); however as previously discussed, ALK-positive patients were significantly younger than ALK− patients. When they controlled for age, there were no differences in FFS or OS [12]. Table 5.1 reviews the clinical features and outcomes for both ALK+ and ALK− patients. Both the IPI and the prognosis in T-cell lymphoma' scoring system are predictive of progression-free survival (PFS) and OS survival in ALCL [12]. In addition, expression of CD56, a neural cell adhesion molecule, was shown in a series of 143 patients with ALCL to be a predictor of poor survival (approximately 5-year OS: 28% vs. 65%, $P=0.002$) [43]. The inferior outcome associated with CD56 was seen with ALK+ and ALK− patients.

Immunophenotype

ALCL frequently do not stain with T-cell markers. Up to 75% are CD3 negative, and staining is variable with CD2, CD5, CD4, and CD8 [12, 44]. Virtually all ALCL are positive for CD30 [45]. The small cell variant of ALCL may display positive staining only on the less numerous larger cells and not on the smaller lymphocytes. ALCL may express cytotoxic T-cell markers, including

Table 5.1 Clinical Features and outcomes of ALCL based on ALK status

Clinical feature	ALK+	ALK−	*P*[a]	PTCL-NOS	*P*[b]
Total no. patients (%)	87 (55)	72 (45)		331	
Median age, year	34	58	<0.001	57	0.30
Age less than 60 years, no (%)	74 (86)	42 (58)	<0.001	170 (50)	0.21
Male–female ratio	1.7:1	1.5:1	0.74	1.01	0.41
Stage no. (%)					
ll	30 (35)	30 (42)	0.38	102 (31)	18
lll	25 (29)	15 (21)		87 (20)	
IV	31 (30)	27 (37)		145 (43)	
Elevated LDH, no. (%)	31 (37)	31 (46)	0.28	158 (49)	0.62
Performance status >2, no. (%)	30 (35)	21 (30)	0.56	60 (18)	0.02
Nodal only disease, no. (%)	39 (54)	38 (49)	0.52	124 (42)	0.07
Extranodal sites >1, no. (%)	17 (19.5)	15 (21)	0.84	99 (29)	0.15
Bulky disease >10 cm, no. (%)	17 (21)	6 (11)	0.17	19 (7)	0.25
B Symptoms, no. (%)	52 (60)	41 (57)	0.72	118 (35)	<0.001
Hemoglobin less than 110 g/L, no. (%)	17 (27)	18 (32)	0.54	61 (22)	0.11
Platelets less than 150×10^8/L, no. (%)	6 (10)	6 (11)	0.83	64 (24)	0.03
IPI score, no. (%)					
0, 1	40 (49)	27 (41)	0.50	88 (28)	0.066
2	18 (22)	13 (20)		111 (35)	
3	12 (15)	16 (24)		71 (22)	
4, 5	12 (14)	10 (15)		48 (15)	
5-year FFS (%)	60	36	0.015	20	0.012
5-year OS (%)	70	49	0.016	32	0.032
5-year FFS by IPI, (%)					
0, 1	80	62		35	
2	61	44	0.022	16	
3	23	15		13	
4,5	25	13		8	
5-year OS by IPI %					
0, 1	90	74		52	
2	68 ($P < 0.001$)[c]	62	<001[c]	33	<0.001[c]
3	23	31		16	
4, 5	33	13		13	

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[a] is statistical comparison between Alk+ and ALK-
[b] is statistical comparison between Alk- and PTCL

perforin, granzyme-B, and TIA-1 [46]. EMA may also be expressed in some cases.

ALK positivity in ALCL is due to rearrangement of the ALK gene located at chromosome 2p23. The most common partner is the NPM gene located at chromosome 5q35 resulting in the (2;5)(p23;q35) translocation [47] followed by the non-muscle tropomyosin gene 3 located at chromosome 1q25 resulting in the (1;2)(q25;p23) translocation [46]. Inversion of the ALK gene, Inv(2)(p23q35), also is seen in a small number of cases, and other fusion partners have also been identified [46]. The NPM/ALK fusion protein constitutively activates a number of intracellular pathways, including phosphatidylinositol 3-kinase-AKT, JAK/STAT, and RAS/MEK/ERK.

Treatment of Systemic ALCL

Chemotherapy

The standard treatment for most patients with systemic ALCL has been CHOP-based chemotherapy. Outcomes using CHOP and related aggressive lymphoma regimens can be derived from large intergroup studies. The GELA has reported results from their trials in which systemic ALCL patients were treated with combination chemotherapy regimens including ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) followed by a consolidation phase with high-dose methotrexate, ifosfamide, etoposide, asparaginase, and cytosine-arabinoside or m-BACOD (methotrexate, bleomycin, cyclophosphamide, vincristine, dexamethasone), VIMMM (VM26, ifosfamide, mitoxantrone, methyl-gag, methotrexate)/ACVBP, and CHOP [48]. In those studies, the ALCL patients, not stratified for ALK expression, had a CR rate of 69% and OS of 63% at 5 years. In a retrospective report, Falini et al. examined the outcomes according to ALK expression in 78 patients [40]. Overall survival was better for ALK+ patients when compared to ALK− (71% vs. 15%), and 10-year DFS was 28% for ALK− vs. 82% for ALK+ patients. ALK+ patients with intermediate or high IPI had a worse outcome compared to low IPI ALK+ patients (OS 94% vs. 41%).

Addition of etoposide to CHOP has been explored in a number of trials for patients with aggressive T- and B-cell NHL. In the NHL-B1 trial added etoposide to CHOP in younger patients improved overall survival and disease-free survival in T-cell patients, but results were not significant for ALCL patients due to small numbers [49]. The NHL-B2 explored a more aggressive regimen (CHOP-14 vs. CHOP 21) in older patients (>age 61) and favored the more aggressive regimen, but only 3.5% of patients in this trial had ALCL [50]. In a more recent study from the German High Grade Lymphoma Group in which 78 ALK+ and 113 ALK− patients were randomized to CHOP or CHOEP, the 3-year EFS and OS were 75 and 89% for ALK+ and 45% and 62% for ALK− patients respectively [51]. There was an overall improvement in outcome in OS for the ALK+ patients with the addition of etoposide (3-year EFS 91% vs. 57%, $P=0.12$). However, there was no improvement for patients treated with dose-escalated therapy (Mega CHOEP), and in fact, younger patients who received MegaCHOEP had a worse outcome than those receiving CHOEP-14. In this trial, ALK− patients had a similar outcome to patients with other aggressive nodal PTCL subtypes (PTCLu and AITL). There was a difference in outcome for ALK− patients based on IPI in that the low IPI patients had a favorable outcome, as shown in Fig. 5.2.

Transplantation for ALCL

Autologous Stem Cell Transplant

Autologous stem cell transplant (ASCT) has been a standard treatment for patients in first remission with ALK− ALCL and in first relapse for ALK+ ALCL. Retrospective reviews of autologous transplant data have shown that ALCL patients had the best outcome, with a 3-year DFS of 67% when compared with other T-cell subtypes [52]. The European Group for Blood and Marrow Transplantation reported that patients who were in CR or PR at the time of transplant had better outcomes than those who had chemorefractory disease [53]. The GELTAMO experience with 123 patients with relapsed/refractory T-cell NHL, of which 25% cases were ALCL, demonstrated that intermediate or high IPI, extranodal disease, and elevated β2-microglobulin at time of transplant were associated with inferior survival [54]. No significant survival differences were noted for ALCL compared with other T-cell subtypes, and ALK status was not available. Nickelsen et al. reported results from ASCT in first remission [55]. The most common subtype in this study was ALK− ALCL (39%). Patients were treated with 4–6 courses of dose-escalated CHOP plus etoposide and then ASCT. Sixty-seven percent of the T-cell NHL patients were able to complete therapy without progression.

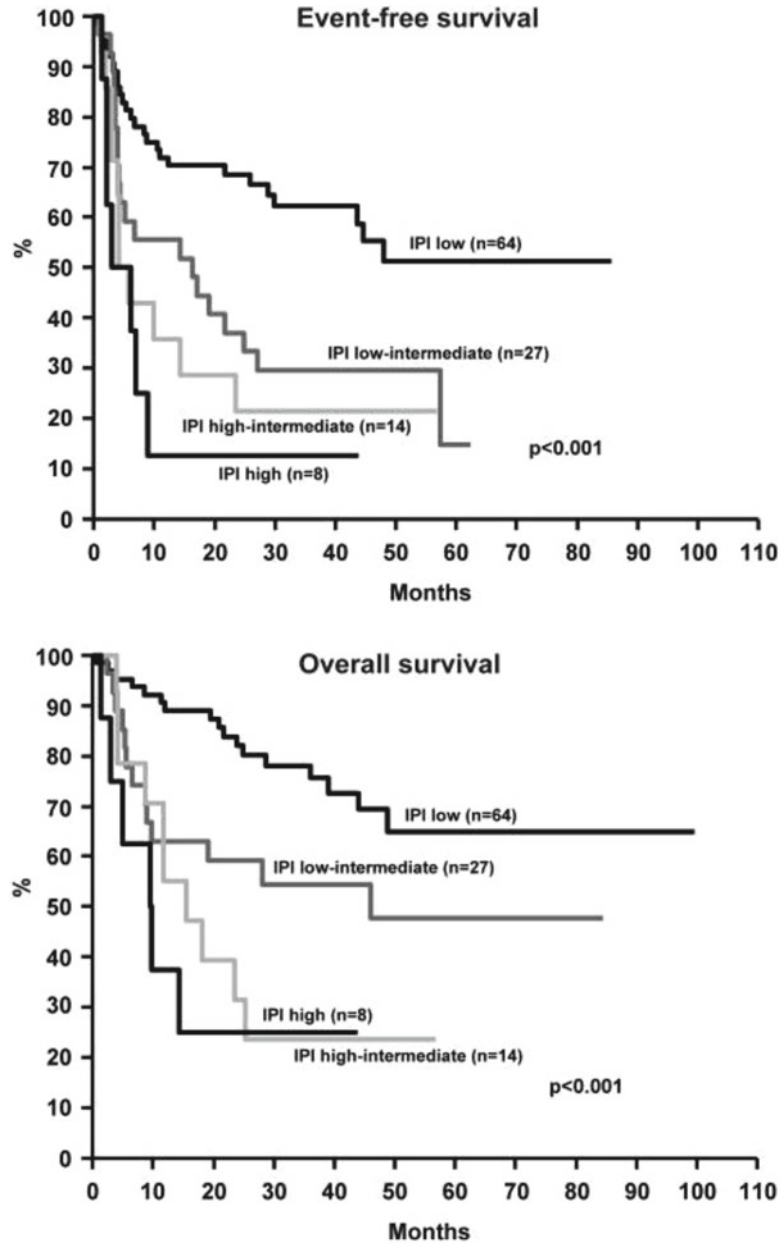

Fig. 5.2 Outcomes based on IPI status for 113 ALK negative ALCL patients after chemotherapy with CHOP or CHOEP in the German High Grade Non-Hodgkins Lymphoma Study Group trials (reprinted from [51], with permission from the American Society of Hematology)

Allogeneic Stem Cell Transplant

Allogeneic stem cell transplantation has been used as a treatment modality in patients with relapsed or refractory ALCL, in many cases after ASCT. A French study reported retrospective results for 77 T-cell lymphomas, 35% of which were ALCL [50]. Fifty-seven patients received myeloablative conditioning; 5-year toxicity-related mortality was 33%. The 5-year EFS and OS for the ALCL patients were 48% and 55%

respectively. ALK status did not impact survival. Of note, chemotherapy-resistant patients also appeared to benefit from allo-SCT with 5-year OS of 29% and successful use of donor lymphocyte infusions (DLI) suggested a graft-versus-lymphoma effect. Corradini et al. reported a small series of 17 patients (four ALCL) with relapsed T-cell NHL who received salvage chemotherapy followed by allo-SCT with reduced intensity conditioning and planned DLI [56, 57]. All patients had sustained engraftment; the estimated 3-year PFS and OS rates were 64 and 81%. All four ALCL patients were event-free at 10, 12, 17, and 36 months.

Novel Therapeutics

There are several FDA-approved agents that are clinically active as single agents for relapsed or refractory ALCL. Pralatrexate is a 10-deaza-aminopterin-analog of methotrexate and a novel targeted antifolate that has shown higher affinity to the reduced folate carrier type 1, increased accumulation and polyglutamylation in tumor cells compared to methotrexate. In a phase I/II study of relapsed/refractory lymphoma, the pralatrexate MTD was 30 mg/m^2 weekly for 6 weeks every 7 weeks [58, 59]. Among 26 evaluable relapsed/refractory T-cell NHL patients, the ORR was 54% (47% by intent-to-treat). Two of the eight CRs seen were systemic ALCL patients (one ALK− and one ALK+) lasting 2 and 22+ months. Denileukin diftitox is a fusion protein which targets the high-affinity interleukin-2 receptor. In a Phase II study of denileukin diftitox in relapsed and refractory T-cell lymphoma patients, two of three patients with ALCL responded (both were ALK-) [60].

Histone deacetylases (HDACs) are a novel class of epigenetic agents which modulate gene expression and regulate acetylation of cellular proteins. The mechanism of HDAC inhibitors in T-cell lymphomas is unknown but may be related to pleotrophic effects on multiple intracellular pathways. Both vorinostat (Zolinza) and romidepsin (Istodax) are FDA-approved: vorinostat for the treatment of CTCL and romidepsin for both cutaneous and aggressive peripheral T-cell lymphomas [59, 61]. Piekarz et al. first reported activity for romidepsin in aggressive T-cell lymphomas, with an ORR of 31% with single-agent romidepsin in 48 relapsed/refractory T-cell NHL patients (4 CR and 11 PR) [62]. The median DOR was 9 months (range 2–61+ months). In a pivotal multicenter trial of 131 patients with aggressive T-cell lymphomas, the objective response rate was 25% (33/130), including 15% (19/130) with CR/CRu. The median duration of response was 17 months, with the longest response ongoing at 34+ months. Of 21 ALK− ALCL patients in the trial, five responded (four CR, one PR) [54].

Immunomodulatory drugs (IMiD drugs) such as lenalidomide have been shown to have a number of biological effects, including modulation of cytokine expression and enhancement of antitumor immunity. Activity of thalidomide had been demonstrated in T-cell lymphoma in one report [63]. A trial exploring the activity of single-agent lenalidomide in relapsed/refractory T-cell NHL has reported an ORR of 30% [64]. Clinical trials examining lenalidomide in combination with other agents in T-cell NHL are being initiated.

Targeted agents

CD30 has been a promising therapeutic target in ALCL. Several anti-CD30 antibodies have been developed and have demonstrated limited clinical activity. MDX-060 (Medarex), a fully human anti-CD30 IgG1k monoclonal antibody, was shown to inhibit growth of CD-30 positive tumor cells in vitro and tumor xenograft models [65]. However, clinical activity was modest with an 8% response rate (6/72) [66]. MDX-1401, a second-generation antibody with improved effector function, has been in Phase I trials which are ongoing. SGN-30 (Seattle Genetics), a chimeric anti-CD30 monoclonal antibody, demonstrated a response rate of 17% in patients with systemic ALCL with median response durations ranging from 27 to 1,460 days [67, 68]. In patients with primary cutaneous ALCL, the ORR was 70% [69]. Figure 5.3 demonstrates a complete clinical response in a patient with refractory ALCL.

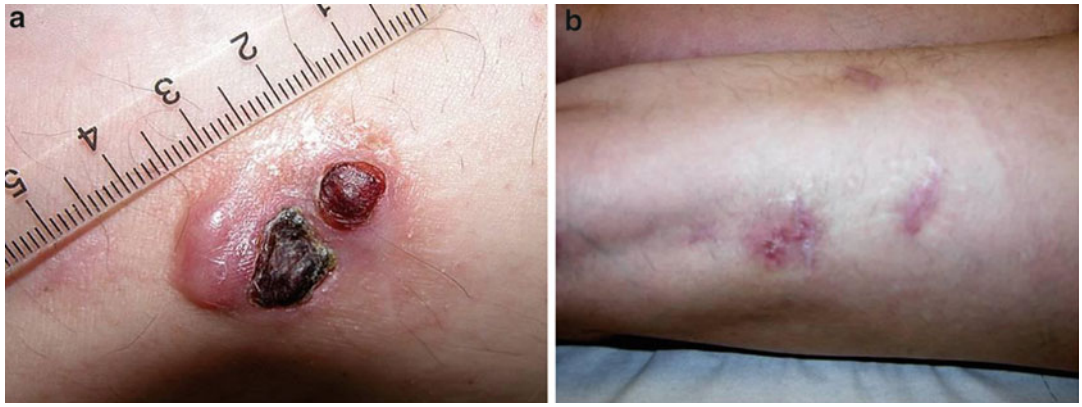

Fig. 5.3 Cutaneous ALCL patient treated with humanized SGN-30 antibody demonstrates complete regression of tumor. (**a**) Pretreatment, (**b**) After six doses of antibody

SGN-35 (brentuximab vedotin) is an antibody-drug conjugate, which was formed by coupling the anti-CD-30 antibody, cAC10, to monomethyl auristatin E (MMAE), an antitubulin agent [68]. In preclinical mouse xenograft models, SGN-35 also induced durable dose-dependent tumor regression compared to either untreated mice or another control group receiving IgG-vcMMAE [68]. In two phase I studies, SGN-35 demonstrated significant clinical activity in relapsed/refractory systemic ALCL [70, 71]. In these trials, 86% of patients (6/7) had documented CR. Subsequently, a phase II multicenter registration trial of brentuximab vedotin was conducted in patients with relapsed or refractory ALCL [72]. The overall response rate was 86% (50 of 58 patients), with CR in 53%. Patients received brentuximab vedotin 1.8 mg/kg q3 weeks for up to 16 cycles. Pts had received a median of 2 (range 1–6) prior systemic therapies, 62% of pts had primary refractory disease, 50% were refractory to their most recent prior therapy, and 22% had never responded to any prior therapy. Median duration of objective response had not been reached but ranged from 0.3 to 45.3 weeks. Fourteen patients moved on to stem cell transplant in remission (seven allogeneic, seven autologous). Peripheral sensory neuropathy was the most frequent side effect and occurred in 36% of patients. The use of brentuximab along with chemotherapy as firstline treatment for systemic anaplastic large-cell lymphomas is under investigation.

Conclusions

The CD30 positive malignancies comprise a spectrum of diseases which include benign cutaneous as well as malignant systemic entities. Cutaneous manifestations are common with systemic anaplastic large-cell lymphomas, which must be clearly distinguished from their more benign cutaneous restricted counterparts. Novel therapeutic approaches for this broad group of diseases target the CD30 antigen and have led to high response rates in relapsed and refractory patients. The appearance of CD30+ lymphomas in the setting of breast implants has recently been observed and these patients may have regression of disease with removal of the implants.

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