Aggressive Epidermotropic Cutaneous CD8+ Lymphoma: A cutaneous lymphoma with distinct clinical and pathological features Report of

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Aggressive Epidermotropic Cutaneous CD8+ Lymphoma: A cutaneous lymphoma with distinct clinical and pathological features.

Report of an EORTC Cutaneous Lymphoma Task Force Workshop

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Abstract

Aims: Aggressive epidermotropic cutaneous CD8+ lymphoma is currently afforded provisional status in the WHO classification of lymphomas. An EORTC Workshop was convened to describe in detail the features of this putative neoplasm and evaluate its nosological status with respect to other cutaneous CD8+ lymphomas.

Methods & Results: Sixty-one CD8+ cases were analysed at the workshop; clinical details, often with photographs, histological sections, immunohistochemical results, treatment and patient outcome were discussed & recorded. Eighteen cases had distinct features and conformed to the diagnosis of aggressive epidermotropic cutaneous CD8+ lymphoma. The patients typically present with widespread plaques and tumours, often ulcerated and haemorrhagic, and have striking pagetoid epidermotropism histologically. A CD8+ CD45RA+ CD45RO- CD2- CD5- CD56- phenotype, with 1 or more cytotoxic markers was found in 7/18 with a very similar phenotype in the remainder.. The tumours seldom involve lymph nodes but mucosae and central nervous system involvement are not uncommon. The prognosis is poor, with a median survival of 12 months. Examples of CD8+ mycosis fungoides, lymphomatoid papulosis and Woringer-Kolopp presented the typical features well documented in the CD4+ forms of those diseases.

Conclusions: Aggressive Epidermotropic Cutaneous CD8+ Lymphoma is a distinct lymphoma that warrants inclusion as a distinct entity in future revisions of lymphoma classifications.

Aggressive Epidermotropic Cutaneous CD8+ Lymphoma: A cutaneous lymphoma with distinct clinical and pathological features.

Report of an EORTC Cutaneous Lymphoma Task Force Workshop.

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Background: The recent WHO-EORTC consensus classification on cutaneous lymphomas included aggressive epidermotropic CD8+ lymphoma (as originally described by Berti et al)

under the "provisional" category. This reflects the paucity of published data with respect to this lymphoma & whether it warrants recognition as a discrete clinico-pathological entity.

Methods: This study collected 71 cases of CD8+ cutaneous lymphoma. The cases were collected for a workshop of the European Organisation for Research and Treatment of Cancer Cutaneous Lymphoma Task Force (EORTC), convened in London, specifically to assess the nosological status of aggressive cutaneous epidermotropic CD8+ lymphoma, and formally assess the clinicopathological features of the CD8 variants of the more common forms of cutaneous T-cell lymphoma.

Results: Of 71 cases, 61 were included in the study. These comprised 18 cases of aggressive cutaneous epidermotropic CD8+ lymphoma, 34 examples of CD8+ mycosis fungoides, 6 cases of CD8+ lymphomatoid papulosis, 2 of solitary pagetoid reticulosis (Woringer-Kolopp) and 1 borderline LyP – anaplastic large cell lymphoma. Patients with aggressive cutaneous epidermotropic CD8+ lymphoma presented with widespread ulcerated plaques and tumours, often haemorrhagic, or in some examples, 2-3 large ulcerated tumours. No patient had a history of patches and plaques, poikiloderma or other characteristic feature suggestive of mycosis fungoides. The median survival of this group is 12 months (cf CD8+ mycosis fungoides group, 31 remain alive with or without disease; $p < 0.002$). The tumour cells had a CD2- CD5- CD45RA+ CD45RO- phenotype in 7 cases, with many more cases varying from this phenotype in just 1 parameter; none labelled with CD56, and there was a proliferative fraction >50% in the 13 of the 18 cases so investigated. CD8+ mycosis fungoides, lymphomatoid papulosis and pagetoid reticulosis did not differ from the usual CD4+ diseases.

Conclusion: Mycosis fungoides and lymphomatoid papulosis with a CD8+ phenotype do not differ from the usual CD4+ forms of the diseases. Aggressive cutaneous epidermotropic CD8+ lymphoma has a characteristic clinical presentation, pathology and prognosis, and is distinct from both classical and CD8+ cases of mycosis fungoides. This justifies its inclusion as a discrete sub-category of cutaneous lymphoma in future revisions of the consensus classification.

Introduction

There has been consensus in the classification of cutaneous lymphoma culminating in the publication of the WHO lymphoma classification with its distinct section of cutaneous lymphomas[1]. This document acknowledges the completely different clinical behaviour and prognosis of many primary cutaneous lymphomas when compared to their counterparts arising at other sites.

While there remains little controversy with respect to mycosis fungoides, Sezary syndrome and primary cutaneous CD30+ lymphoproliferations, the remaining group of diseases, constituting < 10% of cutaneous lymphomas, are more problematic. In particular, a provisional category has been retained for two putative entities, viz. Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma & primary cutaneous aggressive CD8+ T-cell lymphoma. Although there is presumptive evidence to support the inclusion of these as bona fide categories, it has been concluded that more data are required before granting each unequivocal status as a clinico-pathological entity distinct from other forms of cutaneous lymphoma. A meeting of the EORTC was convened in London, in which cases of primary cutaneous CD8+ lymphoma were assembled from many centres across Europe, discussed and, more specifically, the potential status of primary cutaneous aggressive CD8+ T-cell

lymphoma as a disease entity considered. The findings of the conference indicate this lymphoma has distinct clinical, pathological and immunophenotypic features thus supporting the inclusion of this lymphoma as a separate category in future revisions of the consensus classification.

Material and Methods

Cases

A total of 71 examples of CD8+ lymphoma were submitted for inclusion in the study by the members of the EORTC Cutaneous Lymphoma Task Force. The following data were recorded: sex, age at diagnosis, site of manifestation, clinical presentation, involvement of other organs, therapy, length of follow-up and outcome.
Juvenile CD8+ hypopigmented mycosis fungoides has been the subject of several publications, is widely acknowledged as a particular variant of T-cell lymphoma, and no cases were submitted for consideration. Furthermore, subcutaneous T-cell lymphoma was actively excluded as this disease formed the basis of a separate workshop.

Pathology Studies

All biopsy specimens were routinely processed and embedded in paraffin. According to available material, 5µm tissue sections were cut and stained with haematoxylin and eosin, and by immunohistochemistry for the antibodies listed in Table 1. Expression by >75% of cells was defined as positive, <10% negative, 10-75% +/-.

Table 1. Antibodies used for immunophenotyping.

The cases were reviewed and classified by attending pathologists and dermatologists in discussion in a lecture theatre and around a multiheaded microscope. A consensus was defined as no individual author dissented.

Statistical Analysis

Survival time was calculated from the date of histologically confirmed diagnosis until the lymphoma-related death or latest known follow-up using SAS 9.2 statistical package. The cut-off level for statistical significance was set at 0.05 in all analyses.

Results

Definition of Groups

Based on the collected clinical, histological and immunohistochemical data three principal groups were defined. The majority of cases (34) could be classified as CD8+ mycosis fungoides; there were 6 cases of CD8+ lymphomatoid papulosis, 1 of CD8+ lymphomatoid papulosis - cutaneous anaplastic large cell lymphoma overlap and 2 cases of pagetoid reticulosis. Eighteen cases were distinct from these groups and matched the previous descriptions of primary cutaneous aggressive CD8+ T-cell lymphoma. Ten cases were rejected from the study. These were as follows: three cases were either deemed unclassifiable (primary cutaneous T-cell lymphoma NOS according to the EORTC –WHO consensus classification, e.g. an unusual double CD4+ /CD8+ lymphoma arising in an HIV+ patient) or formed isolated sundry albeit well-recognised diseases - HTLV-1+ CD8+ lymphoma and CD8+ ATLL. Seven further cases had insufficient details supplied for inclusion; all these were rejected & took no further part in the study.

Mycosis fungoides (MF) with CD8 phenotype

This group constituted the majority of submitted cases, 20 males and 14 females with a mean age of 49.6 years (males 53, females 46.3 years) (Table 2). A crucial feature of this group was the clinical presentation of patches and plaques typical of classical mycosis fungoides (Figs 1a-c & 1d). The distribution of disease did not differ from classical CD4+ MF.

Table 2 Cases of Mycosis fungoides, Lymphomatoid papulosis and Pagetoid Reticulosis with a CD8+ phenotype

Figs. 1a, b & c. Three examples of patients with patches of CD8+ mycosis fungoides, indistinguishable from classical CD4+ disease.

Fig. 1d. A plaque of CD8+ mycosis fungoides on the lower limb.

Fig. 1e. Tagging of lymphocytes with perinuclear halos along the basal epidermal layer, in a case of mycosis fungoides (H&E x200).

The cases presented the histomorphology usually associated with, and well-documented in, classical MF. Thus, epidermotropism, tagging along the basal epidermal layer (Fig. 1e), Pautrier microabscesses, variable dermal infiltrate of pleomorphic cells having cerebriform nuclear contours were each seen to varying degrees in this group. The dermal infiltrate varied in accord with patch, plaque or tumour stage of disease. No features appeared to distinguish the group from commonplace CD4+ MF.

By definition a majority of tumour cells expressed CD8 (Fig 1f); all failed to react with the CD4 antibody. The majority of cases labelled with one or both of granzyme B and TIA-1. A single case expressed CD56. In 23 cases of CD8+ MF so tested 18 were CD45RO+. Of 15 tested all expressed CD2, whilst of 16 tested 11 labelled with CD5. Ki-67 was assessed in 19 and revealed a low proliferative fraction (10- <50%) in all.

Similarly, following a variety of accepted treatment regimens commonly used in mycosis fungoides survival time mirrored the more common CD4 form of the disease (Fig. 1g); all but two patients are still alive, having received a variety of standard therapies after a median of 47 months. Treatments included; PUVA, UVB, topical steroids, nitrogen mustard, radiotherapy, methotrexate, miltefosine, cyclophosphamide, gemcitabine, alpha-interferon, bexarotene, TSEB & CHOP.

Fig. 1g. Survival curves of patients with CD8+ mycosis fungoides & aggressive epidermotropic CD8+ lymphoma

Lymphomatoid Papulosis.

These 6 patients presented with groups of ulcerating papules and nodules, which characteristically waxed and waned, in the typical manner of LyP (Table 2). In two cases the lesions had a haemorrhagic appearance, but otherwise did not differ appreciably from classical LyP. All patients followed a benign clinical course, having been treated with standard therapeutic regimens, which included simple follow up, PUVA & methotrexate.

Histologically, a wedge-shaped infiltrate with a mixed population of cells, including large atypical mononuclear CD30+ cells, was seen in 4 cases, with a further case having sheets of anaplastic cells typifying type C. In a single case the infiltrate comprised smaller CD30- cells akin to those seen in MF, typical of LyP type B. One additional case was

classified as LyP/ALCL overlap, and presented as a solitary nodule, which regressed. Histologically there was a dense population of CD30+ CD8+ T-cells with relatively few admixed inflammatory cells. The patient remains well. None of the cases conformed to the recently described lymphomatoid papulosis type D, in which the CD8+ lesional cells infiltrate the epidermis with a pagetoid reticulosis pattern.

Solitary pagetoid reticulosis (Woringer-Kolopp)

Two patients presented with solitary hyperkeratotic erythematous patches characteristic of the solitary form of pagetoid reticulosis, a recognised variant of MF. Histologically, there was marked pagetoid epidermotropism of medium-sized atypical mononuclear T-cells. Neither patient has progressive disease, with each responding to local directed therapy, UVB and steroids (Table 2).

Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma

In 18 cases there was consensus that the lymphoma differed substantially from cases included in the previous groups. The clinical details of this group of patients are summarised in Table 3a. These patients were mainly adult with 11 males & 7 females, and a mean age of 54.5 years (males 51.6, females 59.4; range 27-87). The clinical presentation not only differed from usual MF, lacking the patches and plaques that define that disease, but displayed lesions that had many similar features. Lesions were located in multiple sites including the trunk, arms and legs, and face. Mucosal (oral) disease was noted at presentation in 2 cases. Ulcerated crusted and nodular lesions were most common, often with haemorrhagic foci. Infiltrated plaques or tumours manifest early in the disease (Figs. 2a-g); Clinical follicular involvement was not a feature commented upon in any case. In two patients a limited number of tumours, particularly on the face, led to the patient presenting (Fig. 2h). No patient gave a long history of scaly patches or poikiloderma to suggest an evolution from a more indolent prodromal period. One patient had a history of rheumatic fever and a clinical diagnosis of vasculitis was initially made. Staging procedures, in 17 patients, including chest X-rays, abdominal, chest and total body CT scans, revealed enlarged lymph nodes in only one instance at presentation, found to be reactive on biopsy, confirming the lesions to be primary cutaneous. Bone marrow investigations in all patients failed to reveal involvement by disease. In 13 cases the patients rapidly succumbed to the disease, with a median survival of 12 months. A variety of therapies had been used in these patients; 13 patients underwent chemotherapy or immunotherapy, with or without radiotherapy or PUVA. While a few patients enjoyed a partial response, only 1 had a complete response recorded, who then subsequently relapsed and died. Two patients underwent autopsy examinations: in one, no evidence of visceral disease was found; the other had widespread involvement of liver, lungs, spleen, heart and mediastina lymph nodes. HIV status was negative in the 10 patients investigated; HTLV-1 status was assessed in 4 and was negative. Survival differed significantly from the MF group, with a median survival of 12 months ($p < 0.002$) (Fig 1g).

Table 3a Primary Cutaneous Aggressive Epidermotropic CD8+ Lymphoma

Figs. 2a-g. Presentations of aggressive epidermotropic CD8+ lymphoma included widespread ulcerated plaques and tumours, a) often haemorrhagic; b) haemorrhagic plaques on the chest and trunk & limbs of these patients: c) ulcerated tumours & plaques (same patient as "a": d) deeply ulcerated tumour: e) Disseminated ulcerated

haemorrhagic plaques. This patient had no visceral disease at autopsy; f) haemorrhagic necrotic plaques: g) Ulcerated tumours on the head and trunk.

Fig. 2h. Aggressive epidermotropic CD8+ lymphoma; a solitary periorbital mass, clinically mimicking extranodal NK/T-cell lymphoma and blastic plasmacytoid dendritic cell neoplasm.

Biopsies had been taken from a variety of clinical lesions, and this was reflected in the histology. Thus, ulceration was common, being observed in 14 patients. Erythematous hyperkeratotic plaques typically revealed hyperkeratosis and/or acanthosis, and striking epidermotropism. The epidermotropism was a conspicuous observation in 15 cases, conforming to a pagetoid reticulosis pattern i.e. single atypical cells liberally replacing the epidermis albeit most concentrated in the lower portion (Fig 3a-d). Pautrier microabscesses were conspicuously lacking despite the number of malignant cells, only being noted in two cases, and then a minority feature; similarly, lining of atypical cells along the epidermal basal layer – "tagging" - was never an observation; the epidermis was simply liberally peppered by individual atypical cells akin to that seen in solitary and diffuse forms of pagetoid reticulosis. Folliculotropism was noted in 8 cases of 11 in which follicles were well seen (Figs. 4a &b), with a similar pattern of single cell infiltration, albeit often florid, but mucinous degeneration of follicles was absent, and follicular disease was in all cases overshadowed by the interstitial and epidermal infiltrate; malignant cells permeated between eccrine glands in 5 cases of 8 in which these were clearly visualised but syringotropism proper was not convincing, present focally in a single case (Figs. 5a &b). A diffuse and dense dermal population of pleomorphic cells was found in biopsies of the clinical tumours. Angiocentricity was a common finding (Figs. 6a-d), observed in 11 biopsies, sometimes accompanied by angiodestruction. Ischaemic necrosis within the dermis was pronounced in 2 cases and ischaemic necrosis of the epidermis in 5. The dermal infiltrate consisted of medium-sized but quite monotonous atypical cells in the vast majority of cases. The majority of cells in most cases had enlarged hyperchromatic rounded nuclei frequently with a coarse chromatin pattern (Fig.7). The cerebriform nuclear contour, the hallmark of MF, was not present in the majority of cells in any case, although perinuclear halos were often seen. Nodular collections of large highly pleomorphic/anaplastic cells that characterise "high grade" transformation in MF were not seen in any case.

Figs. 3a-d. A pagetoid reticulosis pattern of epidermotropsim was characteristic of aggressive epidermotropic CD8+ lymphoma, without Pautrier microabscesses in the vast majority of biopsies (H&E, x200)

Figs. 4a & b. Histological folliculotropism was common, although clinical follicular disease was not conspicuous clinically (H&E, x 200).

Figs. 5a & b. Permeation of sweat glands was often seen (a) but convincing syringotropism proper only found focally in one case (b) (H&E x 200).

Figs. 6a-d. Ischaemic changes, including epidermal (a) and dermal (b) necrosis reflected the common finding of angiocentricity (d), sometimes with vasculitis/angiodestruction (d) (H&E, x100, x200, x40, x200 respectively).

Fig. 7 Tumour cells of aggressive epidermotropic CD8+ lymphoma were mostly medium sized, and whilst markedly atypical, never large or blastic (H&E, a x200, b x400).

A variable interstitial component, and occasional subcutaneous extension, without adipocyte rimming, were other unremarkable sundry observations.
The results of immunophenotyping these cases are presented in Table 3b. Several characteristic traits emerged within this group. Most (14) cases lacked CD2 and/or CD5, and expressed CD45RA (14 cases, Figs. 8a-d). Conversely, only 3 of 17 presented a population of cells that labelled with antibody to CD45RO, and in these few cells were positive. Of 10 cases investigated for Beta-F1 expression, 8 were positive in the tumour cells. A high proliferative fraction with Ki-67 was found in all but 2 cases investigated. The neoplastic cells in each case expressed one or both of TIA-1 or granzyme B; none expressed CD30 or CD56. All tumours were negative with in-situ hybridisation for EBER.

Table 3b Immunophenotype of Primary Cutaneous Aggressive Epidermotropic CD8+ Lymphoma cases*

Figs 8a-d. Immunocytochemistry in cutaneous aggressive epidermotropic CD8+ lymphoma: a) diffuse expression of CD8 b) CD45RA and c) loss of CD5 expression.: d) a high proliferative fraction with Ki-67 was characteristic (x100).

Discussion.

The literature reports of "CD8+ lymphomas" suggest a markedly variable patient outcome. Agnarsson et al divided CD8+ lymphomas into progressive and indolent groups. The former presented with infiltrated plaques and nodules, the latter had chronic patches typical of mycosis fungoides (2). Other authors emphasise, either the aggressive nature of CD8+ lymphoma (3,4), a benign clinical course and/or that CD8 expression by neoplastic cells cannot be assumed to impart a poor prognosis (5, 6,7,49, 61). Hagiwara et al studied a series of CD8+ epidermotropic lymphomas and found spontaneous regression in 80% with only 1 fatality of 5 patients (8). However, little clinical description was provided, and the possibility of lymphomatoid papulosis types D & E (31; see below) not considered.

Recent classifications of primary cutaneous lymphomas have emphasised the collective importance of clinical, pathological and immunophenotypic parameters in delineating disease entities. Mycosis fungoides, lymphomatoid papulosis and CD30 lymphoproliferation, the most common T-cell lymphoid neoplasms, have well-established clinical features and pathological morphologies. There remain a group of rarer malignancies in which a paucity of data has undermined attempts to definitively assess nosological status and clinicopathological details. In 1999, Berti et al reported a series of 17 patients with cytotoxic lymphoproliferative disorders, variably characterised as lymphomatoid papulosis, anaplastic large cell lymphoma, mycosis fungoides and cases of a hitherto unreported aggressive epidermotropic form of CD8+ disease (9). These latter cases differed from the more common mycosis fungoides clinically and histopathologically. Since then there have been a number of isolated reports that attest to this distinctive entity (10, 11,12, 13, 14, 15, 16, 50). It is accepted that MF, LyP and anaplastic large cell lymphoma may, exceptionally, display a cytotoxic phenotype. In such cases successful diagnosis rests on careful clinical and histological appraisal; thus, these diseases present the "usual" clinical and histological features of these disorders and simply differ in the cytotoxic phenotype of the neoplastic cells. Nevertheless, formal evaluation of these variants and comparisons with the provisionally accepted aggressive epidermotropic cytotoxic lymphoma of Berti has been wanting.

In this paper, the clinical, histological and immunphenotypic characteristics of forms of CD8+ cutaneous lymphoproliferative disease have been collected and analysed. These proliferations encompass mycosis fungoides, lymphomatoid papulosis, anaplastic large cell lymphoma, Woringer-Kolopp and the provisional entity aggressive epidermotropic cytotoxic lymphoma.

Of the cases submitted, 34 had the classic clinical phenotype of mycosis fungoides (MF). Thus, nothing in the presentation and clinical appraisal distinguished these patients from commonplace CD4 disease. Indeed, the first and only unusual characteristic was the finding of a CD8 immunophenotype on biopsy material. The other immunocytochemical findings were largely unextraordinary; a single case was CD56+, and the observation of T-cell antigen loss, when observed, did not conform to a particular pattern. MF is believed to represent a neoplasm of memory T-cells, reflected in the usual immunoexpression of CD45RO by the malignant cells. This contrasts with "native" CD45RO- but CD45RA+ T-cells. In the limited previous formal studies, < 9% of MF cases display immunopositivity for this marker (17); a higher fraction was observed in this series - 5 of 23 labelled with CD45RA. Most patients in the study group followed a protracted, relatively benign, course in accord with classical CD4 MF. The findings herein convincingly indicate CD8+ MF to be indistinguishable from the usual CD4+ form of disease, differing only in the single immunphenotypic anomaly; furthermore, they are in agreement with previous authors who contend that CD8 expression, in and of itself, cannot be taken to imply a poor prognosis. (18, 6, 19), 20, 21, 22, 23, 24). The same assertion has been made with regard to the CD4- CD8- variant of otherwise typical MF (25) and CD56+ disease (51). Thus, careful clinical assessment for characteristic patches & plaques, or other hallmarks of MF e.g. follicular mucinosis, hypopigmentation or poikiloderma, are of critical importance for accurate diagnosis.

Similar observations obtain with respect to CD8+ variant lymphomatoid papulosis (LyP), cutaneous anaplastic large cell lymphoma (ALCL) and the solitary form of pagetoid reticulosis (Woringer-Kolopp). Interestingly, the presence of haemorrhagic lesions was commented upon in several cases. A characteristic wedge-shaped infiltrate of ulcerated skin, containing markedly atypical CD30+ T-cells completed an almost identical picture to classical LyP. The clinical observation of haemorrhage was reflected in evidence of this histologically. All patients remain alive and well in accord with the benign prognosis of typical LyP, and the reports of previous examples of CD8 LyP (26, 27). Previous literature reports attest to the similarity of the CD8+ form of primary cutaneous ALCL to the classical CD4 disease, including the favourable prognosis (28, 27, 29, 30, 52). Lymphomatoid papulosis type D is a relatively recently distinct form of LyP (31), clinically identical to other forms of LyP, but distinctive in the pagetoid reticulosis pattern of epidermotropism and CD8+ phenotype. Similarly, LyP type E commonly has a CD8+ phenotype, and displays an angiocentric histology (62). Thus, the differential diagnosis of these forms of LyP include aggressive epidermotropic CD8+ lymphoma; distinction between these two requires attention to clinical details and the presence or absence of CD30+ atypical cells. None of the cases of LyP in this series was of this type; furthermore, no patient in the aggressive CD8+ epidermotropic lymphoma group had a clinical history of waxing and waning papules or nodules to indicate associated LyP of any form, nor did they express CD30.

The clinical appearance of the solitary form of pagetoid reticulosis, Woringer-Kolopp, accounted for 2 cases submitted. Approximately half of reported cases of pagetoid reticulosis are CD8+ (33, 53). The clinical observations of solitary scaly erythematous acral plaques, the striking histological epidermotropism are typical, and the disease did not progress in either patient.

The remaining 18 cases of CD8+ lymphoma did not conform to mycosis fungoides, lymphomatoid papulosis or pagetoid reticulosis. Nevertheless, they were distinctive clinically, histologically and immunophenotypically. Of the 18 cases, 16 patients initially presented with widespread, often haemorrhagic plaques and extensive tumours.

Immunohistochemically, all cases had a CD8+ CD4 - EBV - CD56 – phenotype. There is a suggestion of a CD2- CD5- CD45RO- CD45RA+ phenotype, this collective pattern being observed in 7 cases. In the physiological transition from naïve (CD45RA+) to memory (CD45RO+) T-cells there is up-regulation of the adhesion molecule, CD2, and therefore a relationship between the expressions of these immuno-markers may be expected. Agnarrson was the first to suggest that loss of CD2 expression correlates with a poor prognosis, but this is likely to reflect that such cases in that series were genuine aggressive epidermotropic CD8+ lymphoma, as opposed to the "chronic form" of CD8+ lymphoma viz. mycosis fungoides (2). Although neoplastic cells in MF are typically memory T-cells, and therefore CD45RO+ CD45RA-, the latter can be seen in a small minority of cases (the vast majority of which are CD4+), without an adverse prognosis in the few studied (17). Indeed, the switch between CD45RA and RO is not irreversible, particularly in the absence of continual antigen stimulation. (54). A markedly high proliferative fraction was reflected in at least 50%, often >75%, of malignant cells labelling with MIB-1 (to Ki-67 antigen) in 13 of 17 so investigated, a feature uncommon in tumour MF unless transformation has supervened. This has been noted previously (11,12,13).

The basis for this aggressive behaviour remains speculative. Urosevic et al postulate that the expression of HLA-G, a non-classical HLA class Ib molecule restricted to immunoprivileged sites, may act to down-regulate the host natural anti-tumour response resulting in rapid evolution of disease. They found expression of this molecule in all four cases of CD8+ lymphoma tested (35). Nevertheless, the variability of prognosis between different forms of CD8+ lymphoma e.g. in comparison to juvenile hypopigmented MF, emphasise the situation is, perhaps, more complex (6, 18, 19).

These cases are distinct from known and accepted forms of cutaneous lymphoma. One proffered interpretation is that these tumours represent an aggressive form of mycosis fungoides. However, the cases of CD8+ MF in this series, and others, convincingly demonstrate that clinically typical CD8+ MF follows a natural course of progression identical to the commonplace CD4+ disease (24).

Furthermore, the relatively short history of widespread ulcerated haemorrhagic nodules and tumours is not the usual clinical presentation of MF, but invites a different differential diagnosis, including cutaneous γδ lymphoma and Ketron-Goodman disease. Most circulating T-cells express the αβ chain in the T-cell receptor with < 5% of the γδ subtype. The latter are the neoplastic cell in the aggressive γδ lymphoma, which may present a clinical picture very similar to primary cutaneous CD8+ lymphoma, and has a similarly dismal prognosis. Cutaneous γδ lymphoma, however, has a CD4- CD8- CD56+ immunophenotype in the vast majority of instances (37); moreover, by definition, the malignant cells will be negative for the beta chain of the T-cell receptor. Although two of the cases in this series were also negative for beta-F1, this does not prove that the malignant T-cells were of γδ type, as the antigen may simply fail to be expressed. In both cases the malignant cells had a CD8+ CD56- phenotype, which is not that typically seen in γδ lymphomas. Furthermore, a frozen section of one of these tumours was also negative for T-cell receptor δ. Nevertheless, although in the majority of cases the tumour cells of γδ lymphomas are CD8-, a small

physiological population of CD4- CD8+ γδ T-cells is known to exist (38, 55). The possibility that some cases of primary cutaneous CD8+ lymphoma are a rare form of γδ cutaneous lymphoma can not always be excluded; nevertheless, most examples of γδ lymphoma are CD56+, not seen in any of our cases, and immunolabelling for beta-F1 excludes those tested in our series.

A few case reports do suggest that in rare cases, this aggressive lymphoma can be preceded by a lengthy prodromal period (39, 40), although in Ito et al the histology of the original lesions dating 10 years previously had not been presented or discussed; moreover, the relationship of the lymphoma to the long history of psoriasis in Weenig et al is uncertain. At least one case has been linked to HTLV-1 infection, (41) although the authors' did not demonstrate viral integration into neoplastic cells. Finally, a single case with anomalous expression of CD15 has been reported (42). Interestingly, the possibility of therapy inducing a CD8+ lymphoma, or worsening prognosis in this lymphoma, has been postulated by several authors (14, 56) & attributed to augmentation of Th1 immunity.

Previous reports by some of the authors (1,9) have indicated the difficulties in making the distinction between aggressive epidermotropic CD8+ lymphoma and other forms of CD8+ T-cell lymphoma. However, the analysis of this large series indicates that other recognisable forms of CD8+ T-cell lymphoma present diagnostic histological features not seen in any of these cases eg CD30 expression in lymphomatoid papulosis & anaplastic lymphoma. Conversely, unlike MF, there are few or no Pautrier microabscesses despite considerable epidermotropism, there is a pagetoid reticulosis pattern of epidermotropism and the neoplastic cytology is more monotonous than is usual in MF. Finally, immunhistochemistry suggests distinct phenotypes.

Patients with the disseminated form of pagetoid reticulosis (Ketron-Goodman disease) present with multiple ulcerated plaques and tumours at various sites, similar to patients in our series, and often have a poor prognosis (43, 44, 45). It is likely that many patients diagnosed with disseminated pagetoid reticulosis have either aggressive epidermotropic CD8+ or cutaneous γδ lymphoma; a minority may represent rare examples of aggressive MF. Previous reports of disseminated pagetoid reticulosis detail variable phenotypes, including a CD4- CD8- phenotype (43, 44, 45, 57, 58) (and may, therefore, represent γδ lymphomas), and CD8+ CD4- (43, 59, 60) (therefore representing aggressive epidermotropic cutaneous CD8+ lymphoma).

The two patients that presented with more limited tumorous facial lesions had an appearance that resembled extranodal NK/T-cell lymphoma and blastic plasmacytoid dendritic cell neoplasm. Both are readily excluded by the immunophenotype; in particular, the absence of EBV expression is an exceptional event, if seen at all, in NK/T-cell disease. A single case of aggressive epidermotropic CD8+ lymphoma mimicking extranodal NK/T-cell lymphoma has been previously reported (46). In one patient there were more widespread plaques on the trunk, and there was subsequent rapid development of multiple plaques and tumours in the other patient.

Recently, a report of two cases and review of the literature by Nofal et al, proposed diagnostic criteria for aggressive epidermotropic CD8+ cutaneous lymphoma (47). Our data support many of the suggested criteria; for diagnosis, we emphasise the acute presentation of plaques/tumours, often ulcerated/haemorrhagic, mucosal involvement is not rare; histologically, the finding of a pagetoid reticulosis pattern of epidermotropism, and angiocentricity, together with a CD8+ CD45RA+ phenotype, Ki-67 > 75%; either CD56(-) or

betaF1+, and expression of one or more of TIA-1 or granzyme B. Whilst not a constant finding, focal or complete loss of one of CD2 or CD5 is also common; previous reports have documented a similar pattern. Proposed diagnostic criteria are listed in table 4.

Cutaneous lymphomas should be considered, in terms of diagnosis and management, on the collective bases of clinical appearance, pathological findings and immunophenotype rather than any of these parameters in isolation. It is the view of the workshop panel that, on current evidence, aggressive epidermotropic CD8+ lymphoma has a recognisable clinical presentation, histopathology and immunphenotype, and should be classified as a specific lymphoma in future revisions of the WHO lymphoma classification. Finally, in view of the very poor prognosis, a multicentre clinical trial using aggressive therapy might be considered in the future to try & improve survival for patients with this disease.

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Table 1.Antibodies used for immunophenotyping.

Antibody specificity	Species & type	Clone	Source	Conditions
CD2	Mouse IgG1	AB75	Novocastra	EDTA; 1/40
CD3	Rabbit, monoclonal	2GV6	Ventana	EDTA; pre-diluted
CD4	Rabbit, polyclonal	SP35	Ventana	EDTA; pre-diluted
CD5	Mouse, IgG1	4C7	Novocastra	EDTA; 1/50 dilution
CD8	Rabbit, monoclonal	SP57	Ventana	EDTA; pre-diluted
CD7	Mouse, IgG2b	LP15	Novocastra	EDTA; 1/20
CD45RO	Mouse, IgG2A	UCHL-1	BioGenex	1/200
CD45RA	Mouse, IgG1	4KB5	DakoCytomation	1/50; citrate
CD56	Mouse, IgG1	1B6	Novocastra	EDTA; 1/50
TIA-1	Mouse, IgG1	2G9A10F5	Beckman Coulter	1/200; citrate
Granzyme B	Mouse, IgG2A	11F1	Novocastra	1/30; citrate
BetaF1	Mouse, IgG1	8A3	ThermoScientific	1/15; trypsin
MIB-1	Mouse, IgG1	MIB-1	DakoCytomation	1/5; citrate

Table 2 Cases of Mycosis fungoides, Lymphomatoid papulosis and Pagetoid Reticulosis with a CD8+ phenotype

Age/sex	Clinical features	Therapy	Outcome	Time period*
54 male	patches buttocks 35 years	Chemo	A+D	48 months
MF				
19 male	papules on limbs	DXT	A+W	68 months
MF				
42 male	erythematosus lesions buttock	DXT	A+W	72 months
MF				
74 male	purpura legs	NK	A+D	22 months
MF				
26 female	10 patches hips/arms	Topical	A+D	22 months
MF				
31 male	scaly papules	PUVA	A+D	36 months
MF				
56 female	erythematous papules	Chemo	A+W	12 months
MF				

	23 female	petechial patches	DXT	A+D	120 months
MF					
	39 female	poikiloderma, sacral tumour	DXT, PUVA	A+D	47 months
MF					
	52 male	poikiloderma, plaques	Chemo/DXT	A+D	180 months
MF					
	40 male	erythrodermic, HIV+	Chemotherapy	Died of disease	7 months
Erythrodermic MF					
	58 female	erythematous hyperkeratotic lesions	Chemotherapy	Unknown	NA
MF					
	55 female	psoriasioform patches/plaques	PUVA, Chemo	Died of disease	132 months
MF					
	60 male	eczematous lesions – plaques/nodules	PUVA, retinoids	A+D	120 months
MF					
	30 male	poikilodermatous scaly lesions	PUVA, Chemo	A+D	132 months
MF					
	89 male	psoriasioform patches	NR	A+D	16 months
MF					
	50 female	atrophic patches buttocks	UVB	A+D	72 months
MF					
	30 female	erythematous scaly patches	PUVA	A+W	30 months
MF					
	43 female	atropic patch buttock	DXT	A+W	42 months
MF					
	51 male	patches buttock/hip	local steroids	A+D	60 months
MF					
	49 male	generalised patches	PUVA	A+W	120 months
MF					
	51 male	patches on back	PUVA	A+D	360 months
MF					
	44 male	atropic patches arms/legs	PUVA	A+W	43 months
MF					
	39 female	generalised patches	PUVA	A+D	40 months
MF					
	69 male	patches axillae/groins	PUVA	A+W	11 months
MF					
	82 male	scalp erosions, plaques, nodules	DXT	A+D	36 months
MF					
	65 male	patches and plaques	Steroids	A+D	49 months
MF					
	46 male	scaly patches	PUVA	A+D	72 months
MF					
	52 female	Widespread patches	PUVA	A+D	36 months
MF					
	62 male	poikiloderma	PUVA	A+D	24 months
MF					
	56 female	patch on thigh	topical	A+W	36 months
MF					
	46 female	psoriasioform patches,plaque arms	DXT	A+D	36 months
MF					
	55 female	generalised patches	PUVA, DXT	A+D	72 months
MF					
	50 male	patches/plaques	Many therapies	A+D	72 months
MF					
	51 male	ulceronecrotic lesions arm/leg	local steroids	A+W	34 months
LyP					
	38 male	ulceronecrotic lesions arm/hip	-	A+W	10 months
LyP					

	24 female	self-healing papulonodular lesions	-	A+W	120
months	Ly				
	72 female	2 papulonecrotic lesions	Excision	A+W	30
months	LyP/ALCL				
	17 female	exudative nodules face,chest	Steroids	NK	NA
	LyP				
	43 male	ulcerated nodule + papule buttock	Excision	A+W	24
months	LyP				
	29 female	relapsing papules/nodules	UVB	A+W	72
months	LyP				
	61 male	solitary gluteal lesion	Excision	A+W	24
months	Woringer-Kolopp				
	46 female	solitary erythematous plaque	DXT	A+W	30
months	Woringer-Kolopp				

A&D = alive with disease; A&W = alive and well; NK – not known; NA = not applicable.

Table 3a Primary Cutaneous Aggressive Epidermotropic CD8+ Lymphoma

Case	Age/sex Time period*	Clinical features Diagnosis	Staging	Therapy	Outcome
1	43 male 7 months	6 weeks widespread ulcerated lesions Aggressive epidermotropic	N***	Chemotherapy	Died of disease
2	32 male 22 months	3/12 ulcerated tumours trunk/extremities Aggressive epidermotropic	N	Chemotherapy	A+ D
3	NK/ male 12 months	disseminated ulcerated tumours Aggressive epidermotropic	N	Chemotherapy	Died of disease
4	27 female 84 months	plaques/nodules Aggressive epidermotropic	ND	DXT	Died of disease
5	58 female 12 months	disseminated plaques/nodules Aggressive epidermotropic	N	PUVA, Chemo	Died of disease
6	80 female	patches/plaques - papules/nodules	N	PUVA/IFN	Died other
causes	NA	Aggressive epidermotropic			
7	53 male 27 months	nodules arm/face/chest Aggressive epidermotropic	N**	PUVA/DXT	Died of disease
8	70 female 36 months	papulunecrotic tumours face/trunk Aggressive epidermotropic	N**	Chemotherapy/DXT	Died of disease
9	87 female 11 months	haemorrhagic tumour orbit Aggressive epidermotropic	N	IFN	Died of disease
10	33 male 10 months	ulcerated patches,plaques, nodules Aggressive epidermotropic	N	Chemotherapy	Died of disease
11	31 male 24 months	palaques/nodules Aggressive epidermotropic	N**	PUVA, Chemo, BXT	Died of disease
12	59 male 28 months	erosive plaques Aggressive epidermotropic	N	HN2	Died of disease
13	55 female 43 months	necrotic tumour elbow Aggressive epidermotropic	N	DXT	A+W
14	27 male 7 months	generalised ulcerated nodules/tumours Aggressive epidermotropic	LN+	Chemotherapy	Died of disease
15	72 male 10 months	ulcerating tumour elbow Aggressive epidermotropic	N	DXT	Died of disease
16	39 female 66 months	ulcerating tumour ear Aggressive epidermotropic	N	DXT	Died of disease
17	67 male 6 months	ulcerating tumours legs Aggressive epidermotropic	N	Chemotherapy	Died of disease
18	74 male 12 months	ulcerated nodules leg/trunk Aggressive epidermotropic	N	IFN, Chemo	Died of disease

*From diagnosis to listed outcome.
NA – not applicable ND not done NK not known
DXT – radiotherapy, IFN – interferon chemotherapy, BXT – bone marrow transplantation
N – negative, LN + lymph node enlargement
** - developed systemic disease *** - autopsy revealed only cutaneous disease

Table 3b Immunophenotype of Primary Cutaneous Aggressive Epidermotropic CD8+ Lymphoma cases*

Case	CD 2	CD5	CD7	CD45RO	CD45RA	MIB-1	Beta-F1
1	-	+/-	-	+/-	+	+	+
2	+/-	+	-	ND	ND	+++	+
3	-	+	-	+/-	+	+	-
4	-	-	-	ND	ND	+++	ND
5	-	+	+	-	+	++	+
6	-	-	+	-	+	+++	+
7	ND	ND	+	ND	+	+++	+
8	-	-	-	-	+	+++	-**
9	+	-	+	-	+	++	+**
10	-	-	-	-	+	+++	+
11	-	-	+	-	+	++	+
12	+	+	ND	-	+/-	ND	ND
13	-	-	-	-	+/-	+++	ND
14	+	+	-	+	+	+++	ND**
15	-	-	+	-	+	+++	ND
16	-	-	+	-	+	+	ND
17	-	-	-	ND	-	ND	ND
18	ND	ND	-	-	+	+++	ND

*All cases were CD8+, CD4-. None labelled with CD56 or antibodies to LMP, and all were negative with in-situ hybridisation for EBER.

T-cell antigens:
+ = at least 75% cells positive
- = less than 10% cells positive
+/- = between 10-75% cells positive

MIB-1:
+ = 25-50%
++ = 50-75%
+++= >75%
** Immunohistochemically negative for T-cell receptor δ on frozen section.
All cases demonstrated T-cell clonality by analysis of T-cell receptor.

Table 4 Proposed diagnostic criteria for the diagnosis of Primary Cutaneous Aggressive Epidermotropic CD8+ Lymphoma

Clinical features	Histology	Immunohistochemistry
Plaques and tumours	Pagetoid reticulosis pattern	CD8+ CD56(-)
No history of patches, evidence of follicular mucinosis or poikiloderma	+/- apoptotic keratinocytes	At least 1 of CD2(-), CD5(-) or CD45RA(+)
	Monomorphic atypia	Ki-67> 50%
		BetaF1(+) or TCR δ(-)
Staging confirms only cutaneous disease		EBER(-)
No immunosuppression		