ORIGINAL ARTICLE

CD56-positive haematological neoplasms of the skin: a multicentre study of the Cutaneous Lymphoma Project Group of the European Organisation for Research and Treatment of Cancer

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Background: Cutaneous lymphomas expressing CD56, a neural cell adhesion molecule, are characterised in most cases by a highly aggressive clinical course and a poor prognosis. However, prognostic subsets within the CD56+ group have been difficult to identify due to the lack of uniform clinicopathological and immunophenotypical criteria.

Methods: A multicentre study was conducted by the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer to define prognostic parameters and establish diagnostic and therapeutic guidelines for CD56+ haematological neoplasms presenting primarily in the skin.

Results: Four different subtypes of lymphoproliferations with CD56 expression were identified: (1) haematodermic neoplasm; (2) skin infiltration as the first manifestation of CD56+ acute myeloid leukaemia; (3) nasal-type extranodal natural killer/T-cell lymphoma; and (4) "classical" cases of cutaneous T-cell lymphoma (CTCL) with co-expression of the CD56 molecule. Patients in the first three groups had a poor outcome (93% died) with a median survival rate of 11 months (95% CI 2–72 months), whereas all patients with CD56+ CTCL were alive at the last follow-up.

Conclusion: Results show that CD56+ cutaneous lymphoproliferative disorders, with the exception of CD56+ CTCL have a very poor prognosis. It is therefore clinically important to separate CD56+ CTCL from the remaining CD56+ haematological disorders.

Cutaneous T-cell lymphomas are a heterogeneous group of malignancies with mycosis fungoides and Sézary syndrome as the common subtypes. Application of monoclonal antibodies against the neural cell adhesion molecule CD56 has led to the recognition of further lymphoma subtypes.[1–3] CD56 was initially identified as a surface molecule of CD16+ natural killer (NK) cells with the morphology of large granular lymphocytes. CD56 is expressed not only on all NK cells but also on subsets of CD4+ and CD8+ T cells.[4] The WHO–EORTC (World Health Organization–European Organisation for Research and Treatment of Cancer) classification distinguishes between several types of CD56+ neoplasms, including nasal/nasal-type extranodal NK/T-cell lymphoma and haematodermic neoplasm (blastic NK-cell lymphoma).[5]

Extranodal NK/T cell lymphoma is a tumour occurring in the nasopharyngeal area and frequently shows an angiocentric growth pattern with prominent necrosis leading to the highly characteristic midline perforation once referred to as "lethal midline granuloma".[6] Most cases are positive for CD56 and Epstein-Barr virus (EBV), and the tumour cells often express cytotoxic molecules such as perforin, granzyme B and TIA-1.

Haematodermic neoplasm is a recently recognised entity characterised by blastoid tumour cells expressing CD4 and CD56; it has a high incidence of skin involvement and harbours the risk of leukaemic dissemination. Although this tumour has been regarded as an NK-cell neoplasm, recent studies suggest that it derives from plasmacytoid dendritic cells (pDC).[7 8] Both CD56+ malignancies—extranodal NK/T cell lymphoma and haematodermic neoplasm—are associated with a highly aggressive clinical course, and thus a poor prognosis. Although systemic chemotherapy is the first choice for both diseases, the results are often disappointing.[9 10]

However, occasionally CD56 may be also expressed by other types of disease with involvement of the skin, such as primary cutaneous CD30+ lymphoproliferations, including lymphomatoid papulosis and anaplastic large cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, or myeloid leukaemia with cutaneous infiltration.[11 12] Physicians face a challenge in diagnosing and treating this group of well-defined types of lymphomas/leukaemia expressing the CD56 molecule. It is uncertain whether these patients have a worse prognosis than patients with extranodal NK/T-cell lymphoma (nasal/nasal type) and haematodermic neoplasm/blastic NK cell lymphoma, and therefore might require a more aggressive therapeutic approach.[12]

To unravel possible clinical differences among the CD56+ cutaneous disorders we conducted a multicentre study to comparatively analyse the clinical features and histomorphology of this group of CD56+ skin lesions. The aim of this study was to define prognostic parameters and guidelines for the diagnosis and treatment of CD56+ haematological neoplasms first presenting in the skin.

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Table 1 Antibodies used for immunophenotyping

Marker	Clones used for staining	Manufacturer
CD3		Dako
CD3e	PS1	Novocastra
CD4	1F6	Novocastra
CD45RO	OPD4	Dako
CD8	C8/144/3	Dako
CD33	WM-54	Dako
CD56	123/C3	Zymed
CD57	F45	Quartett
CD43	DF-T1	Dako
CD34	QBEND10	Immunotech
MPO	A0398	Dako
CD68	KP1	Dako
TIA	TIA-1	Coulter
GranB	Gr-B7	Coulter
CD30	BerH2	Dako
CD123	6H6	eBioscience
EBV-LMP-1	CS1-4	Dako
EBV-EBNA-2	PE2	Dako
TCL-1	27D6/20	Biosearch
TdT	A3527	Dako

MATERIALS AND METHODS
Patients
A total of 34 cases involving European patients with CD56+ lymphoid tumours presenting primarily in the skin were provided by the members of the EORTC Cutaneous Lymphoma Task Force. The following clinical data were recorded: sex, age at first diagnosis, site of manifestation, clinical presentation, time-point of cutaneous involvement, involvement of other organs, concurrent existence of other lymphoid or haematopoietic neoplasias, applied therapy, and outcome.

Pathological studies
All biopsy specimens were routinely processed and embedded in paraffin. Tissue sections (5 μm) were cut and stained with H&E, and for immunohistochemistry using a streptavidin–biotin method using antibodies listed in table 1. For antibodies CD33 and CD123, acetone-fixed frozen tissue sections were stained using the alkaline phosphatase–anti-alkaline phosphatase technique, as previously described.[13]

Cases were reviewed and classified microscopically by each dermatopathologist/pathologist; consensus criteria were established for the diagnosis of questionable cases. Well-established entities such as haematodermic neoplasm/blastic NK cell lymphoma and extranodal NK/T cell lymphoma were defined more strictly and cases with unusual morphology or antigen expression could be identified.

TCR-gamma gene rearrangement studies
DNA used for PCR was extracted from 25 μm paraffin sections after dewaxing and proteinase K digestion using a QIAGEN DNA extraction kit (Qiagen, Hilden, Germany). PCR analysis of T cell receptor gamma (TCR-gamma) chain rearrangements was performed at the participating institutions as previously described.[14 15]

Statistical analysis
Survival time was calculated from the on-study date until the date of lymphoma-related death or the last follow-up. The Kaplan–Meier method was used to calculate survival probability as a function of time. The log-rank test detected significant differences between the survival curves. All data were analysed using SPSS.[16] The cut-off level of statistical significance was set at 0.05 in all analyses.

RESULTS
Definition of groups
Based on the collected clinical, histological, immunohistological, and molecular diagnostic data, four different groups were defined. The majority of cases could be classified in accordance with the WHO and WHO–EORTC classifications—as CD4+/CD56+ haematodermic neoplasm/blastic NK cell lymphoma (group 1) and skin infiltration of CD56+ AML (group 2). In addition, we identified two further subgroups of CD56+ cutaneous disorders, namely, extranodal NK/T cell lymphoma, nasal type (group 3) and CD56+ ''classical'' primary cutaneous T cell lymphomas (group 4) (tables 2 and 3).[5 17]

Group 1: CD4+/CD56+ haematodermic neoplasm (blastic NK-cell lymphoma)
Clinical features
The group comprised 15 men and 5 women (mean age 65 years, range 8–86 years). In most cases, patients presented with multiple red to violet-brown plaques and nodules which occurred mainly in the trunk, head or leg (9/20 patients) or were generalised (8/20 patients) (fig 1A). Three patients had solitary tumours at different localisations, one exhibiting small satellite nodules (fig 1B). In 15/20 cases the tumours presented in the skin, but subsequent systemic disease developed after a short period. Extracutaneous sites, histologically confirmed at biopsy, included bone marrow (13/20), lymph nodes (8/20), blood (4/20), and palate (2/20). Two patients were reported to have concurrent lymphoid/haematopoietic neoplasias (myelodysplastic syndrome and chronic myeloid leukaemia). Despite various chemotherapy regimens, most patients with available follow-up (19/20) died within a few months after diagnosis (median survival 12 months, range 3–55 months, 95% CI 6 to 18 months). Notably, one of the two patients who received allogenic bone marrow transplantation had the longest survival time of 60 months, and the other is still alive.

Histomorphology
The typical characteristics were diffuse monomorphous infiltrates of medium-sized cells separated from the epidermis by a grenz zone. Perivascular patchy infiltrates and an Indian file pattern were occasionally observed. Angiotropism was uncommon (fig 1 C,D).

Immunophenotype
CD4 and CD56 as well as CD43 were expressed by the atypical cells in all cases investigated. The markers characteristic for B/T cell lineage (CD20/CD3), as well as for cytotoxic cell markers TIA1 and GrB, were negative like CD30. CD123 was positive in 6/6 cases where frozen material was available. TCL1 expression (T cell leukaemia antigen) was positive in 4/4 cases investigated. TdT was positive in 5/13 cases. The myelomonocytic markers CD33, MPO (myeloperoxidase), and CD68 were not expressed in 20/20 cases. Tumour cells of all cases were EBV-negative as shown by the absence of LMP-1 (latent membrane protein) and EBNA-2 (fig 1E–G).

Genotype
A clonal TCR-gamma gene rearrangement was not detectable in any of the 15/20 cases investigated, which excluded T lymphocytes as the precursor cell.

Group 2: skin infiltration of CD56+ AML
Clinical features
Three men and one woman (mean age 62 years, range 48–92 years) were investigated in this group. Three patients presented with solitary fast-growing tumours (fig 2A,B), while one patient presented with multiple red to violet tumour nodules. At initial presentation, 2/4 (50%) patients had concurrent bone

Table 2 Clinical characteristics of patients

Characteristics	Group 1	Group 2	Group 3	Group 4
Number	20	4	5	5
Sex				
Male	15 (75%)	3 (75%)	3 (60%)	3 (60%)
Female	5 (25%)	1 (25%)	2 (40%)	2 (40%)
Age (y)				
Mean	65	62	72	54.4.0
Range	8–86	48–92	58–73	7–84
Extent of skin lesion				
Solitary	3 (15%)	3 (75%)	2 (40%)	2 (40%)
Generalised	17 (85%)	1 (25%)	3 (60%)	3 (60%)
Involved extracutaneous sites				
No extracutaneous involvement	0 (0%)	0 (100%)	1 (20%)	5 (100%)
Lymph nodes	13 (65%)	1 (25%)	2 (40%)	0 (0%)
Visceral organs	0 (0%)	0 (0%)	1 (20%)	0 (0%)
Peripheral blood	4 (20%)	1 (25%)	0 (0%)	0 (0%)
Bone marrow	13 (65%)	2 (50%)	1 (20%)	0 (0%)
Palate	3 (15%)	0 (0%)	2 (40%)	0 (0%)
Other neoplasia	2 (10%)*	0 (0%)	0 (0%)	0 (0%)
Therapy				0 (0%)
Phototherapy	0 (0%)	0 (0%)	0 (0%)	1 (20%)
Multiagent chemotherapy	15 (75%)	3 (75%)	4 (80%)	1 (20%)
Radiotherapy	2 (10%)	1 (25%)	1 (20%)	
Bone marrow transplantation	2 (10%)	1 (25%)	0 (0%)	0 (0%)
Survival, months				
Median	12	11	7	+62
Range	3–55	3–60	2–72	
Current status				
No evidence of disease	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Alive with disease	0 (0%)	0 (0%)	1 (20%)	5 (100%)
Died of lymphoma	19 (95%)	4 (100%)	4 (80%)	0 (0%)
Died of other cause	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Group 1, haematodermic neoplasm; group 2, cutaneous infiltrates of acute myeloid leukaemia; group 3, extranodal NK/T-cell lymphoma; group 4, ''classical CTCL'' with expression of CD56.
*One patient developed in addition a chronic myeloid leukaemia, and another patient a myelodysplastic syndrome.

marrow, lymph node, and blood involvement. All patients died after a median survival of 11 months (range 3–60 months, 95% CI 0 to 42 months). Notably, the only patient who received allogenic bone marrow transplantation had the longest survival time of 60 months.

Histomorphology
The tumour cells were monomorphous and medium to large-sized with round nuclei and fine diffuse chromatin. The infiltrate was located mainly in the middle and deep dermis, sparing the subepidermal region, and infiltrated the collagen bundles (fig 2C,D).

Immunophenotype
The neoplastic cells were negative for CD3, CD30 and TIA, but positive for CD4, CD33, CD43, CD56, CD68 and MPO. Interestingly, CD123 was positive in one of the two cases investigated (fig 2E–G). TCL1 was expressed in 2/3 cases. The tumour cells were negative for LMP-1 and EBNA and thus EBV-negative.

Genotype
A clonal TCR-gamma gene rearrangement was not detectable in any of the four cases, which excluded T lymphocytes as the cell of origin.

Table 3 Immunophenotypic and genotypic features of CD56+ lymphoproliferations

Antigen	Group 1	Group 2	Group 3	Group 4
CD3	0/18 (0%)	0/4 (0%)	3/5 (%)	4/5 (80%)
CD3ϵ	2/12 (%)	0/2 (0%)	2/3 (%)	1/2 (50%)
CD4	20/20 (100%)	4/4 (100%)	3/5 (%)	0/5/(0%)
CD8	0/20 (0%)	0/3 (0%)	1/5 (%)	4/5 (80%)
CD30	0/20 (0%)	0/4 (0%)	0/5 (0%)	2/5 (40%)
CD33, MPO, CD68	0/20 (0%)	4/4 (100%)	0/2 (0%)	0/2 (0%)
CD43	17/19 (90%)	4/4 (100%)	1/2 (0%)	0/2 (0%)
CD123	6/6 (100%)	1/2 (50%)	0/1 (0%)	0/2 (0%)
TCL1	4/4 (100%)	2/3 (67%)	nd	0/2 (0%)
TIA	0/20 (0%)	0/3 (0%)	5/5 (100%)	4/5 (80%)
GrB	0/5 (0%)	0/2 (0%)	5/5 (100%)	4/5 (80%)
EBV	0/13 (0%)	0/2 (0%)	3/4 (75%)	0/4 (0%)
TdT	5/13 (39%)	0/3 (0%)	0/1 (0%)	0/2 (0%)
Clonal TCR rearrangement	0/16 (0%)	0/3 (0%)	1/4 (25%)	3/4 (75%)

Group 1, haematodermic neoplasm; group 2, cutaneous infiltrates of acute myeloid leukaemia; group 3, extranodal NK/T-cell lymphoma; group 4, ''classical CTCL'' with expression of CD56.
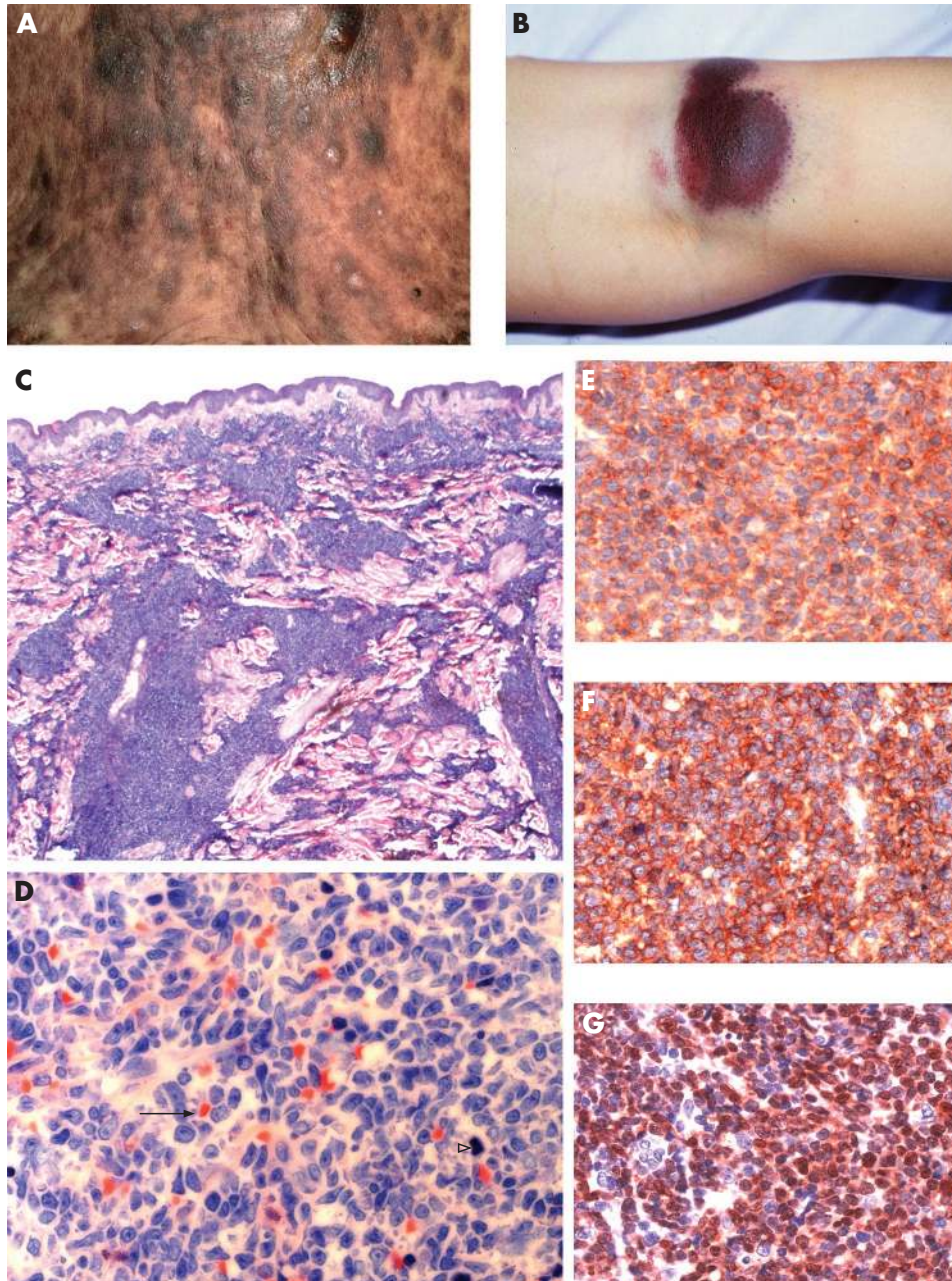MPO, myeloperoxidase; GrB, granzym B; TdT, terminale desoxynucleotidyl transferase.

Figure 1 Morphological and immunophenotypic features of CD4+/CD56+ haematodermic neoplasm (group 1). (A) The trunk of a patient with generalised red to violet-brown plaques and nodules (case 6). (B) Bruise-like lesion on the right knee (case 3). (C and D) Histological findings of skin biopsy show dense infiltration of medium-sized blastoid tumour cells without angiocentric growth pattern, and frequent atypical mitoses (solid arrow) and massive erythrocyte extravasation (open arrowhead). (E) Strong membranous staining of CD56. (F) Strong membranous staining of CD123. (G) Strong nuclear staining of TdT.

Group 3: nasal-type extranodal NK/T cell lymphoma
Clinical features

This category included five patients (three men, two women; mean age 72 years, range 58–73 years). The patients presented either with a fast-growing, solitary tumour on the arm or trunk (2/5) (fig 3A) or with red to brown-violet nodules on the trunk that tended to disseminate (3/5). One patient showed lymph-node and bone-marrow involvement at presentation (case 25). The disease was primarily cutaneous in four of the five cases, but secondary internal involvement included the palate in two cases (fig 3B), the lymph nodes in two, and the liver and bone marrow in one case each. Four patients died shortly after therapy with a median survival of 7 months (range 2–72 months, 95% CI 3 to 12 months). One patient is still alive without extracutaneous disease.

Histomorphology

All cases showed a diffuse, angiocentric and angiodestructive pattern of medium to large-sized atypical lymphocytes (fig 3C,D). Epidermotropism was also seen in 3/4 cases. Coagulative necrosis and apoptotic cells were common.

Immunophenotype

In 5/5 cases, CD56 and cytotoxic markers (TIA1, GrB) were expressed by the atypical cells (fig 3E–G), whereas markers typical for B cells (CD20), as well as for the myelomonocytic lineage (CD33, MPO, CD68) were negative. Markers of EBV-infection (LMP-1, EBNA-2) were expressed by the tumour cells in 3/4 cases. Atypical cells lacked the expression of CD4, CD8, and CD30 and were positive for cytoplasmic CD3 and/or CD3ε in two cases.
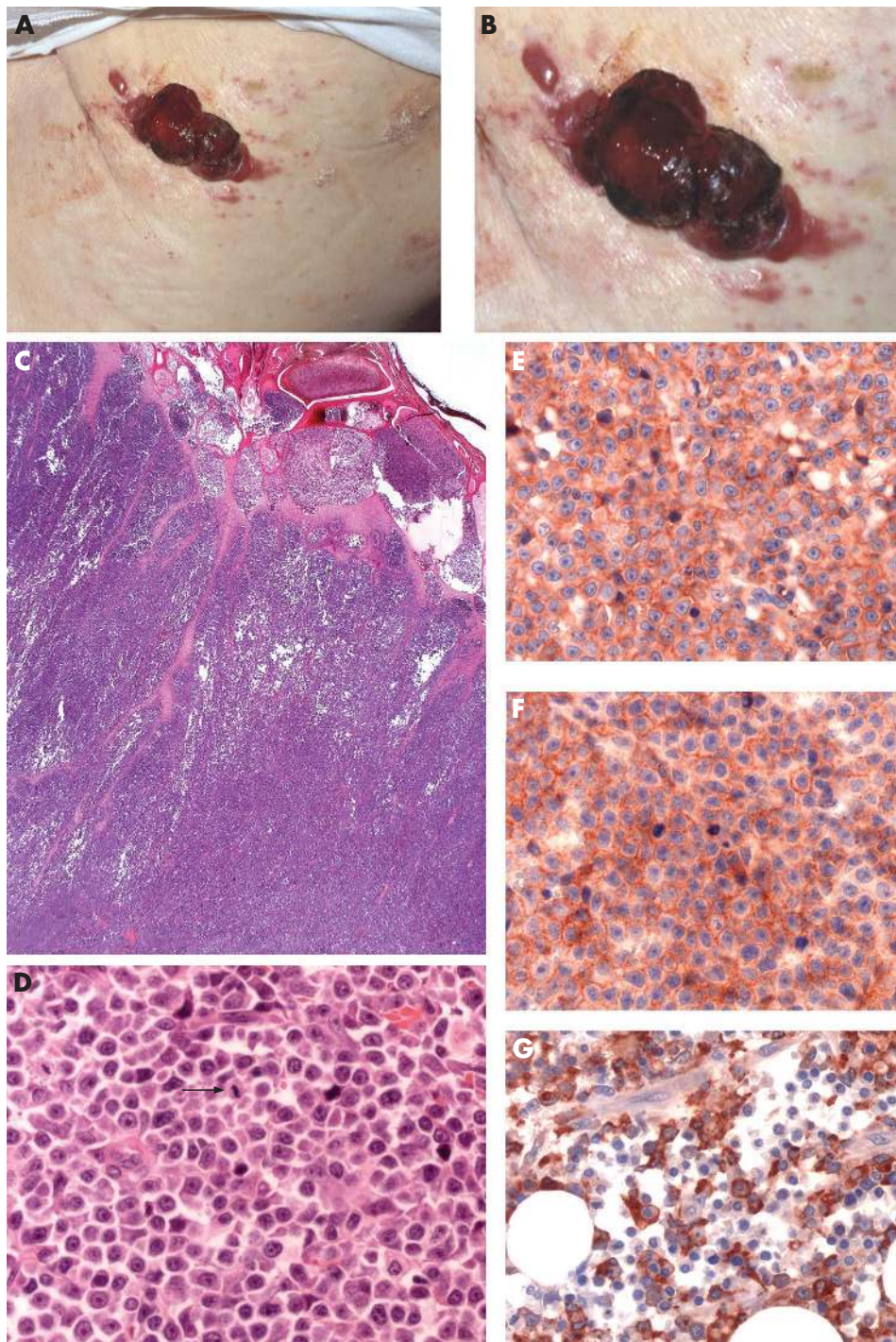
Figure 2 Morphological and immunophenotypic features of cutaneous infiltration of CD56+ AML (group 2). (A and B) Haemorrhagic tumour on the trunk (case 22). (C and D) Histology revealed diffuse infiltration of medium-sized blast like cells with numerous mitoses (arrow). (E) Strong expression of CD4. (F) Strong expression of CD56. (G) Strong expression of MPO.

Genotype
A clonal TCR-gamma gene rearrangement was detectable in one of the four cases investigated.

Group 4: ''classical'' primary cutaneous T cell lymphomas with CD56 co-expression
Clinical features
This group comprised five patients (three men and two women; mean age 54.4 years, range 7–84 years). Two patients presented with the typical recurrent papules and nodules seen in cases of lymphomatoid papulosis (fig 5A); one case displayed

generalised hypo- and hyperpigmented lesions of mycosis fungoides. Two patients showed subcutaneous tumours typical of panniculitis-like T-cell lymphoma. Tumours were of the primary cutaneous type in all cases, and systemic spread was not reported. All patients were alive at the time of evaluation (median follow-up time 62 months).

Morphology and immunophenotype
CD56 expression of the atypical cells was seen in all cases. Four of five cases displayed a cytotoxic phenotype with expression of CD8 and/or TIA-1 and GrB (fig 4B–D). The two cases of
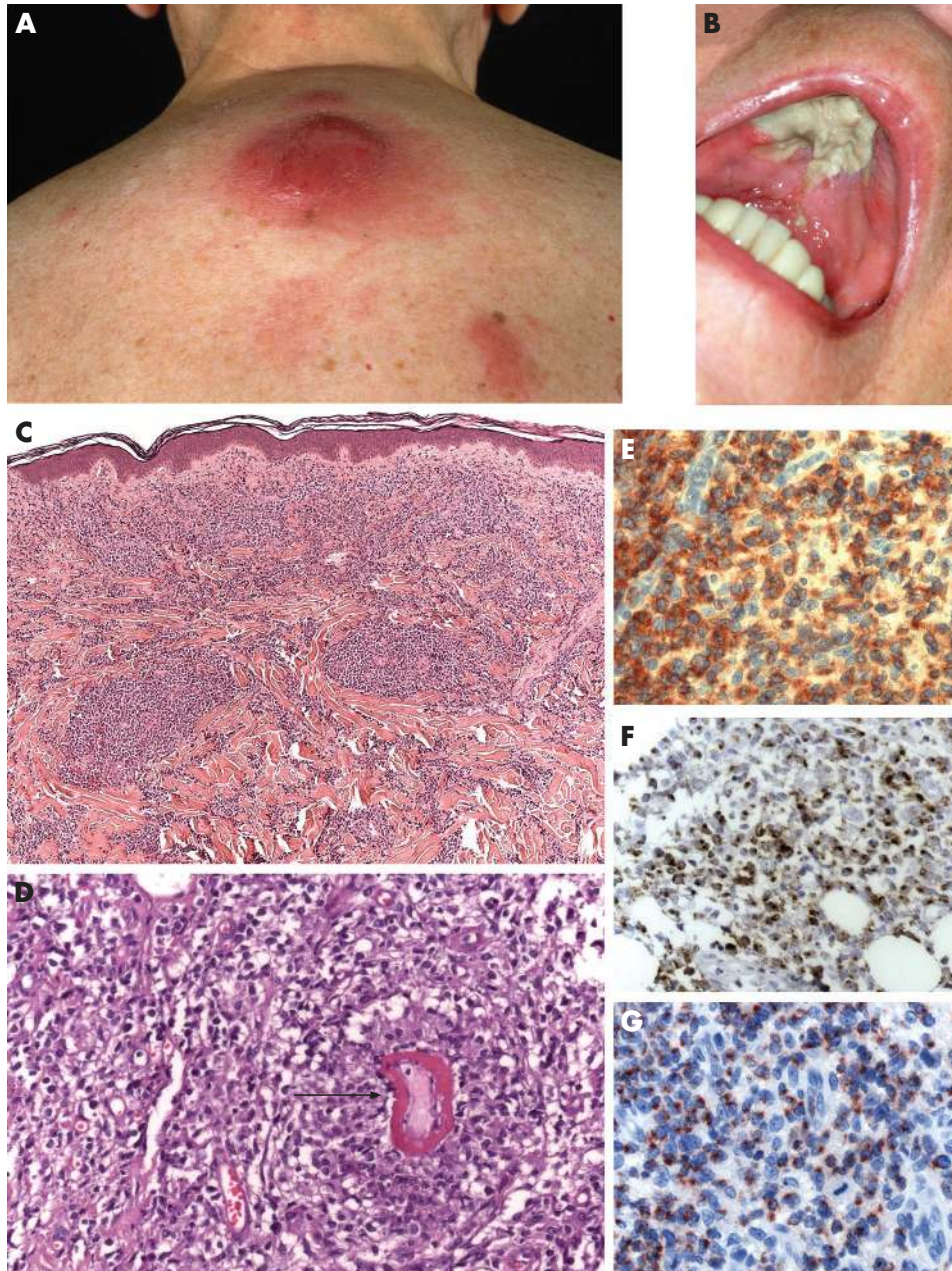
Figure 3 Morphological and immunophenotypic features of extranodal NK/T-cell lymphoma (group 3). (A) Solitary violets tumour on the back; and in addition, (B) infiltration and destruction of the hard palate leading to extensive necrosis (case 29). (C and D) Histological findings show beneath a free grenz zone a prominent angiocentric growth of medium to large blastic lymphocytes, focally with invasion of the blood vessel (arrow). (E) Strong membranous staining of CD8. (F) Cytoplasmic expression of cytotoxic molecules (Gran B). (G) Cytoplasmic expression of cytotoxic molecules (TIA-1) (G).

subcutaneous panniculitis-like T-cell lymphoma displayed an α/β-phenotype. Case 30 with lymphomatoid papulosis had lost CD3, as well as CD4 and TCL1. The tumour cells of all four cases displayed no EBV infection (LMP-1−, EBNA-2−).

Genotype
A clonal TCR gene rearrangement was detectable in all three cases investigated, indicating the T-cell origin of the tumour cells.

CD56 expression in haematological cutaneous malignancies as an indicator of an unfavourable prognosis
Patients in groups 1–3 had an adverse clinical outcome, whereas patients in group 4 displayed an excellent clinical

course (p = 0.0042; log-rank test, fig 5). All 29 patients in groups 1–3, with the exception of one patient, died of disease (median survival probability 11 months, 95% CI 2 to 72 months). In contrast, all patients in group 4 were alive at the last follow-up (5/5, 100%).

DISCUSSION
The spectrum of cutaneous lymphomas expressing CD56 has been heterogeneous with respect to clinical presentation and course, morphology and immunohistochemical phenotype, as well as the association with EBV infection. To classify these neoplasms more precisely, we evaluated the clinical and histological/immunophenotypical characteristics of a large series of CD56+ haematological cases (n = 34) presenting in the skin. Based on the data obtained, we identified four groups
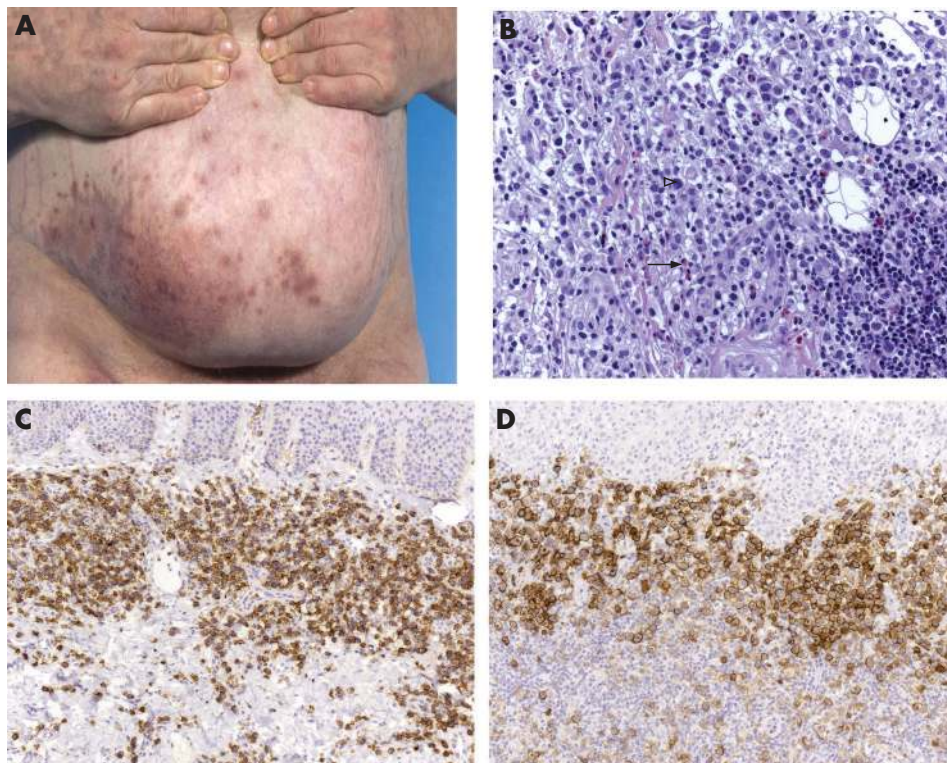
Figure 4 Morphological and immunophenotypic features of lymphomatoid papulosis with co-expression of CD56. (A) Grouped papules on the right abdomen (case 30). (B) Histological findings are large atypical lymphocytes (open arrowhead) embedded in a mixed inflammatory infiltrate with eosiniophilic granulocytes (closed arrow). (C) Immunohistology revealed expression of CD30. (D) Immunohistology revealed expression of CD56.

which show significant differences in clinical behaviour and prognosis.

Despite their different cellular origin, CD56+ cases of haematodermic neoplasm/blastic NK-cell lymphoma (group 1), of AML skin infiltration (group 2) and of extranodal NK/T-cell lymphoma nasal type (group 3) are characterised by their extremely poor clinical outcome. This is in sharp contrast to the very favourable clinical outcome of patients with ''classical'' CD56+ primary cutaneous T-cell lymphoma (group 4).
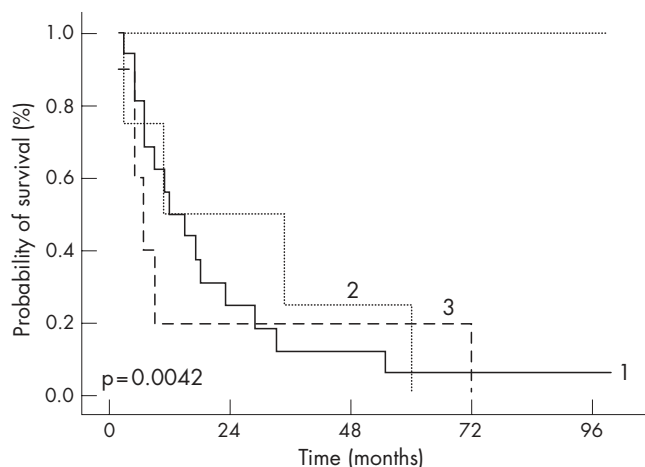

Figure 5 Prognosis of CD56+ haematolymphoid neoplasm. Overall survival showed by Kaplan–Meier survival curves, given by different types of cutaneous CD56+ neoplasm. (1) CD4+/CD56+ haematodermic neoplasm (n = 20). (2) Cutaneous CD56+ AML (n = 4). (3) Extranodal NK/T-cell lymphoma (n = 5). (4) ''Classical cutaneous T cell lymphoma'' with co-expression of CD56 (n = 5) (log-rank test p = 0.0042).

Haematodermic neoplasms (blastic NK-cell lymphomas) (group 1) represent the largest group of our series (20/34, 56%), with a striking male dominance (15/20, 83%). Clinically, all patients experienced an aggressive clinical course regardless of whether they presented with localised or disseminated disease (median survival 12 months). This observation is in line with previous studies and is independent of the therapeutic regimens used.[18 19]

The origin of the CD4+/CD56+ tumour cells of the so-called haematodermic neoplasms/blastic NK-cell lymphomas is the subject of a longstanding debate. NK cell precursor, a myelomonocytic precursor or a mixed NK/myelomonocytic precursor have been proposed.[20–22 24] Petrella et al recently suggested a derivation from pDC, as indicated by expression of the interleukin-3 receptor alpha subunit (CD123).[25 26] Moreover, the same group also showed TCL1 expression in a larger series of CD4+/CD56+ haematodermic neoplasms, thus excluding NK cells as the origin of this entity.[7]

The pDC origin of CD4+/CD56+ haematodermic neoplasms was furthermore supported by Hallermann et al and Urosevic et al, who showed the co-expression of CD123 and ''blood dendritic cell antigen'' (BDCA-2) in nearly all investigated cases of cutaneous CD4+/CD56+ haematodermic neoplasm.[27–29] BDCA-2 is a C-type lectin transmembrane glycoprotein that internalises antigen for presentation to T-cells and is specifically expressed by human pDC.[29] The investigation of a newly-generated cell line (CAL-1) derived from a blastic NK-cell lymphoma revealed further convincing results for the pDC origin of this entity.[30]

The second group (4/34) of cutaneous CD56+ neoplasms represents cutaneous infiltrates of acute myelomonocytic leukaemia (AML), as evidenced by their additional expression of myelomonocytic markers such as CD33, CD68 and MPO.[17] The morphological and clinical features are highly similar to the cases of blastic NK-cell lymphoma of group 1. This includes the

observation that allogenic bone marrow transplantation appears to be the most beneficial therapeutic option. These concordant features suggest a possible relation of both neoplasms, which is supported by the fact that in some cases, patients with haematodermic neoplasms/blastic NK cell lymphoma develop myeloid or myelomonocytic leukaemia as also shown in 2/20 patients of groups 1 and 2.[31][32]

Recently several studies have shown that CD56+ expression on AML tumour cells appears to be associated with a shorter period of complete remission and reduced survival as compared to CD56− cases.[33][34] This is in harmony with the finding that CD56+ myeloid leukaemia displays more frequently an extramedullary involvement (skin, lymph node) at initial presentation, suggesting that CD56+ myeloid leukaemia might constitute a distinct biological and clinical disease entity.[24][35][36]

The third group (5/34) identified among the CD56+ cutaneous neoplasms consists of skin involvement of nasal type extranodal NK/T-cell lymphoma. The clinical course of the five patients (80% men) resembled those in previous reports in that the development of skin lesions (fast-growing tumour nodules) was most frequently followed by involvement of the nasopharyngeal region (40%) and lymph nodes (40%), with early dissemination to the bone marrow and liver (20%).[37] Despite intensive combined chemotherapy, patients with cutaneous NK/T-cell lymphoma have an extremely poor prognosis, as most patients die within several months after its onset as also shown in our patients, who died after a median survival of only 7 months.

According to the WHO classification, extranodal NK/T-cell lymphoma is nearly always associated with EBV infection, irrespective of the ethnic origin of the patients, suggesting a pathogenic role for the virus.[17][38–42] However, we could not detect an EBV infection of tumour cells in 25% of the cases. This is in agreement with a recent series of primary cutaneous NK/T-cell lymphomas of Asian and Caucasian patients, which were EBV-negative in most cases (17/52, 33%).[48–50] Interestingly, the histological features of extranodal NK/T-cell lymphomas are indistinguishable among the various sites of involvement.

The cellular origin of the CD4+/CD56+ cells in extranodal NK/T-cell lymphoma has not been completely clarified. In the majority of extranodal NK/T-cell lymphomas, T-cell receptor genes are in germline configuration, consistent with a natural killer cell origin.[43–47] Conversely, clonal TCR-receptor gene rearrangement as evidence for a T-cell origin could be detected in nearly 30% of the investigated cases of cutaneous extranodal NK/T-cell lymphoma.[48–50] The evidence to date suggests that the postulated counterparts of extranodal NK/T-cell lymphoma are probably both cell types, activated NK cells and cytotoxic T lymphocytes, indicating a close relationship to the precursor cell. However, the presence or absence of EBV or TCR rearrangement in extranodal NK/T cell lymphomas seems to have no prognostic significance.

The fourth group (5/34) represents cutaneous neoplasms with a co-expression of the CD56 molecule but not included in the other groups. All cases of group 4 were cutaneous T-cell lymphomas (CTCL) such as lymphomatoid papulosis (n = 2), CD8+ subcutaneous panniculitis-like T-cell lymphoma with an alpha/beta-phenotype (n = 2) and mycosis fungoides (n = 1). However, besides the typical histological/immunohistochemical and molecular features for these lymphomas, an atypical CD56 expression of the tumour cells was detectable.[5]

The most striking feature of the cases of group 4 is their excellent clinical outcome (all patients alive: follow-up time median 62 months) when compared to the clinical course of the CD56+ cases of the other three groups. Considering the heterogeneity and small number of patients in group 4, our results suggests that the expression of CD56 cannot be regarded

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Take-home messages

- Cutaneous lymphomas expressing CD56, a neural cell adhesion molecule, are characterised in most cases by a highly aggressive clinical course and poor prognosis.
- Aggressive types of CD56-positive neoplasms of the skin are represented by haematodermic neoplasm, skin infiltration as the first manifestation of CD56+ acute myeloid leukaemia, and nasal-type extranodal NK/T-cell lymphoma.
- Cutaneous T-cell lymphoma (CTCL), for example panniculitis like T-cell lymphoma, may also show expression of the CD56 molecule, which is not associated with an aggressive clinical course.
- Therefore, it is clinically very important to separate CD56+ CTCL from the remaining CD56+ haematological disorders.

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as a general marker for adverse prognosis identifying the need to discriminate among the patients suffering from CD56+ neoplasms. However, cases previously termed as subcutaneous panniculitis T-cell lymphoma with a gamma/delta phenotype are now described in the recent WHO–EORTC classification as cutaneous gamma/delta-T cell lymphoma and should be distinguished from subcutaneous panniculitis like T-cell lymphoma. Most patients with a cutaneous gamma/delta-T cell lymphoma have an aggressive disease and are resistant to multiagent chemotherapy and/or radiation therapy, showing a median survival of only 15 months.[5]

In conclusion, our findings indicate that CD56+ cutaneous lymphoproliferative disorders comprise a spectrum of different entities with specific clinical and biological features preferentially occurring in men (26/34, 76%). Most of these entities are associated with an aggressive clinical course and poor outcome with a median survival time of only 7–12 months. However, CD56 expression by itself is not a prognostic marker since several types of "classical CTCL" cases may also show a co-expression of CD56. The extreme prognostic difference among the patients with cutaneous CD56+ neoplasms requires a precise diagnostic evaluation in order to identify those patients who presumably benefit from bone marrow transplantation. Because of the rarity of the diseases described in this study and the small number of patients, especially in groups 2–4, multicentre trials should be initiated to determine the most appropriate treatment strategies.

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