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Indolent CD8-positive lymphoid proliferation of acral sites: three further cases of a rare entity and an update on a unique patient

Background: Primary cutaneous indolent CD8-positive lymphoid proliferation is an emerging entity characterized by slowly enlarging papules and nodules that are pathologically comprised of clonal nonepidermotropic medium-sized atypical CD8(+) T-cells. Although the majority of lesions are solitary and located on the ears, bilateral symmetrical presentations have been described and lesions may arise at other peripheral or 'acral' sites. Patients follow a benign clinical course and systemic involvement has not yet been observed. Despite this, some medical practitioners classify such lesions as peripheral T-cell lymphoma, NOS, a category implying aggressive disease.
Objectives: We present three cases seen in our institutions and provide an update on a previously reported unique patient who continues to develop recurrent and multifocal skin lesions.
Results: Systemic disease progression has not been observed, even in the presence of recurrent and multifocal cutaneous disease.
Conclusions: Indolent CD8-positive lymphoid proliferation of acral sites is a distinctive and readily identifiable entity and should be included in the next consensus revision of cutaneous lymphoma classification. Although cases described thus far have followed an indolent clinical course, dermatologists should remain guarded about the prognosis and full staging and longitudinal observation are recommended until this condition is better understood.

Keywords: acral, CD8, indolent, lymphoid proliferation, lymphoma

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In 2007, Petrella et al. reported four patients with slowly enlarging papulonodular lesions arising on one or both ears characterized by a dense and diffuse nonepidermotropic dermal proliferation of clonal monomorphous medium-sized CD8(+) T-cells with irregular blast-like nuclei

and small nucleoli, separated from the overlying epidermis by a grenz zone. Despite the microscopic findings and the cytotoxic immunophenotype of a high-grade lymphoma, an indolent clinical course was observed in all cases with absence of extracutaneous disease at the time of diagnosis and lack of systemic disease progression or dissemination following surgery, radiotherapy or simple observation.[1]

Forty-four further cases of so-called indolent CD8-positive lymphoid proliferation of the ear have since been reported[2–19] or identified, retrospectively[20–22] with the original description widened to include lesions arising on the nose[6,7,13,16,19] and at other acral sites,[14,16,18,21] and some variation in pathological features, whilst maintaining an indolent clinical evolution (Tables 1 and 2). We present three further cases of this enigmatic entity seen in our institutions and provide an update on a previously reported unique case.[16]

Case 1

A 55-year-old female presented in January 2012 with a slowly enlarging 7 mm erythematous papule on the left nasal tip. Her past medical history was unremarkable and she was otherwise well with no B symptoms and no distant cutaneous lesions, lymphadenopathy or hepatosplenomegaly.

An incisional skin biopsy showed a moderately dense monomorphic nonepidermotropic perivascular and interstitial mononuclear cell infiltrate composed of small to medium-sized lymphoid cells with minimal cytologic pleomorphism (Fig. 1A,B). Immunocytochemistry confirmed a CD8(+) (Fig. 1C) CD30(−) TIA-1(+) Granzyme B(−) PD-1(−) (Fig. 1D) ICOS(−) T-cell phenotype without loss of T-cell associated antigens; thus CD2, CD3 and CD5 were all diffusely positive. CD4 and CD56 were negative. A B-cell component was not identified by CD20 or CD79a. *In situ* hybridization for Epstein–Barr virus-encoded RNA (EBER ISH) was negative. The proliferation fraction measured by Ki-67 was approximately 10% (Fig. 1E). T-cell receptor (TCR) gene analysis revealed a monoclonal rearrangement.

The patient declined staging investigations and treatment as the lesion was asymptomatic. She remains well 24 months after her original presentation with no further cutaneous lesions and no evidence of systemic disease progression.

Case 2

A 37-year-old male presented with a lesion on his ear of unknown duration. His past medical history was unremarkable. An excision biopsy showed a superficial and deep perivascular and interstitial monotonous dermal lymphoid infiltrate extending into the subcutis. There was no epidermotropism and a conspicuous grenz zone was present (Fig. 2A). The mononuclear cells were small to medium-sized with mild cytological atypia, manifest by nuclear enlargement and folding, albeit with a fine chromatin pattern.

Immunocytochemistry confirmed a CD3(+) CD8(+) infiltrate with some reduction in CD2 and, to a lesser degree, CD5 expression. TIA-1 (Fig. 2B) and perforin were diffusely expressed. Granzyme B, CD30, EBER ISH and CD56 were negative. Minority populations of CD4(+) and CD20(+) cells were noted. There was a low proliferation fraction with Ki-67, approximately 10–20%. TCR gene analysis confirmed a monoclonal rearrangement.

Staging investigations were not performed. He remains well 11 months after his original presentation with no further cutaneous lesions and no evidence of systemic disease progression clinically.

Case 3

A 55-year-old man presented with a 6-month history of several asymptomatic erythematous papules on the helix of his left ear (Fig. 3A). His past medical history was unremarkable.

A skin biopsy showed a dense nonepidermotropic infiltrate of the dermis consisting of a monotonous population of medium-sized lymphoid cells .The cells formed nodular clusters in the deeper dermis with a perivascular distribution, but no angiodestruction (Fig. 3B,C). There was mild cytological atypia, with nuclear enlargement and nuclear folding, and only occasional inconspicuous basophilic nucleoli. Immunocytochemistry confirmed a diffuse strong CD3(+) CD8(+) CD4(−) immunophenotype (Fig. 3D,E) with preservation of CD2 and CD5 expression. TIA-1 was diffusely positive (Fig. 3F) with considerable perforin expression (Fig. 3G), but Granzyme B, PD-1, ICOS and CD56 were negative. EBER ISH was negative. The proliferation fraction measured by Ki-67 (Fig. 3H) was moderately high at 40%. TCR gene analysis confirmed a monoclonal rearrangement.

Staging investigations with computed tomography (CT) and a bone marrow examination excluded extracutaneous disease. The patient

Table 1. Indolent CD8-positive lymphoid proliferation of acral sites

	Age/Sex	Site	Duration (months)	Histology	TCR clone	Staging	Treatment	Recurrence	Follow-up (months)
Vaillant et al.[2]	45/M	Right shoulder	NK	Signet ring cells	NK	Normal	NK	Right arm, both shoulders	AWD/132
Friedmann et al.[3]	57/F	Widespread lesions	NK	Prototype	Yes	NK	Mechlorethamine, RT, PUVA, interferon alpha	NK	AWOD/86
Eich et al.[20]	56/M	Ear	NK	Prototype	Yes	Normal	RT (PUVA, interferon alpha and PDT tried first)	None	AWOD/10
Khamaysi et al.[21]	55/F	Right foot	17	Prototype	Yes	Normal	RT followed by SE of residual disease	NS	NS
Fika et al.[22]	72/M	Right ear	24	Prototype	NS	Normal	RT	None	AWOD/18
Petrella et al.[1]	61/M	Right ear	9	Prototype	Yes	Normal	RT 40Gy/16#	Left ear at 9 months	AWD/10
	29/F	Left ear	4	Prototype	Yes	Normal	RT 30Gy/20#	None	AWOD/4
	47/M	Both ears	4	Prototype	Yes	Normal	Observation	SE of recurrences at 12, 24 and 30 months	AWOD/168
	51/M	Left ear	6	Prototype	ND	ND	SR 6 months post-biopsy	None	AWOD/14
Li et al.[4]	57/M	Left ear	60	Signet ring cells	Yes	Normal	SE	None	AWOD/28
Beltraminelli et al.[5]	69/M	Both ears	24	Prototype	No	Normal	Declined	None	AWD/7 NK
	61/M	Left ear	NK	Prototype	Yes	NK	SE	NK	NS
	64/M	Both ears	NK	Prototype	Yes	Normal	SE	None	AWOD/28
Suchak et al.[6]	35/M	Left ear	Few months	Prototype	Yes	Normal	RT	None	AWOD/12
	45/F	Nose	3	Prototype	Yes	Normal	RT	None	AWOD/24
Ryan et al.[7]	86/F	Nasal tip	36	Prototype	Yes	Normal	RT	None	AWOD/6
Swick et al.[8]	52/M	Right ear	48	Prototype	Yes	Normal	SE	None	AWOD/20
	41/M	Both ears	Several years	Prototype	Yes	Normal	SE	None	AWOD/20
Geraud et al.[9]	61/M	Left ear	36	Prototype	NS	Minor lymphadenopathy on CT (stable after 6 months)	Observation	None	AWD/12
Zeng et al.[10]	38/M	Right ear	6	Prototype	Yes	Normal	Observation	RT to further lesion detected at 24 months	NS
	78/F	Right ear	1 week	Prototype	Yes	NS	Declined	None	DWOD/48
Butsch et al.[11]	73/M	Both ears	36	Epidermotropism	Yes	Normal	RT	None	NS
Valois et al.[12]	40/M	Right ear	4	Prototype	Yes	Normal	Topical corticosteroid	NK	NK
Milley et al.[13]	87/F	Nose	108	Prototype	Yes	NK	Topical corticosteroid	NK	NK

Table 1. Continued

	Age/Sex	Site	Duration (months)	Histology	TCR clone	Staging	Treatment	Recurrence	Follow-up (months)
Wobser et al.[14]	61/F	Both heels	48	No grenz zone	Yes	Normal	RT	NS	NS
Kempf[15]	48/M	Right buttock (2007), multiple lesions left foot (2010)	NS	Prototype	No	Normal	RT	Recurrence left foot at 10 months (treated with RT), left foot and right retro-auricular area at 13 months (RT and methotrexate)	AWD/48
	87/F	Right lower leg	NS	Prototype	Yes	No lymphadenopathy	RT	None	AWOD/24
	52/M	Right shoulder	NS	Prototype	Yes	Normal	SE	None	AWOD/26
Greenblatt et al.[16]	47/F*	Nose, right hand	14	Prototype	Initial sample failed to amplify, but further samples monoclonal	Normal	RT (electrons) to nose, RT (30Gy/15#) to hand	RT to further lesions on hands and feet at 6 months and later relapses on right thigh, right hand and right nostril	AWD/12
	37/F	Left heel	9	Prototype	Yes	Normal	Electrons (30Gy/15#)	None	AWOD/36
	70/F	Nose	NS	Prototype	Yes	Normal	Curettage and cautery	None	AWOD/9
	70/M	Left heel	29	Prototype	Yes	Normal	RT (8Gy/2#)	None	AWOD/6
	73/F	Nose	NS	Pautrier micro-abscesses	ND	Declined	SE	None	AWOD/8
	68/M	Left ear	18	Pautrier micro-abscesses	No	Declined	SE	None	AWOD/3
Hagen et al.[17]	36/M	Left lower eyelid	8	Prototype	Yes	NS	No residual lesion post-biopsy	None	AWOD/12
	38/M	Left lower eyelid	6	Prototype	Yes	NS	SE	None	AWOD/12
Wobser et al.[18]	61/F	Ear	NS	NS	Yes	NS	SE, RT	None	AWOD/136
	59/M	Ear	NS	NS	Yes	NS	SE, RT	Recurrences left ear, right ear and nose treated with SE and RT	AWOD/117
	61/F	Both feet	NS	NS	Yes	NS	RT	None	AWOD/24
	77/F	Finger	NS	NS	ND	NS	SE	None	AWOD/8
	49/M	Ear	NS	NS	Yes	NS	SE, RT	None	AWOD/4

Table 1. Continued

	Age/Sex	Site	Duration (months)	Histology	TCR clone	Staging	Treatment	Recurrence	Follow-up (months)
Li et al.[19]	42/M	Right ear	14	Prototype	Yes	Normal	RT	None	AWOD/14
	64/M	Right ear	1	Prototype	NS	Normal	RT	None	AWOD/14
	41/M	Left lower lid	3	Prototype	No	Normal	SE	None	AWOD/14
	54/M	Right ear	NS	Prototype	Yes	Normal	SE	None	AWOD/50
	82/M	Right ear	24	Epidermotropism, no grenz zone	NS	Normal	SE	None	AWOD/14
	55/F	Nose	24	No grenz zone	NS	Normal	SE	None	AWOD/26
	41/F	Nose	36	Prototype	No	Normal	RT	Recurrences right ala, right dorsal nose and right helix	AWOD/134
Kluk et al., 2014 (this series)	55/F Case 1	Nose	NK	Prototype	Yes	Declined	Observation	None	AWD/24
	37/M Case 2	Ear	NK	Prototype	Yes	ND	SE	None	AWOD/11
	55/M Case 3	Left ear	6	Prototype	Yes	Normal	Observation	None	AWD/21
	47/F*Case 4	Nose, hands, feet, thighs	Ongoing	Prototype	Yes	Normal	RT	Further recurrences treated with RT and SE, with subsequent addition of interferon alpha	AWD/36

AWD, alive with disease; AWOD, alive without disease; DWOD, deceased without disease; NS, not stated; ND, not done; NK, not known; PDT photodynamic therapy; PUVA, psoralen-ultraviolet A; RT, radiotherapy; SE, surgical excision; SR spontaneous resolution; TCR, T-cell receptor.

Clinical and pathological characteristics of cases reported to date.

*Update on a case previously reported by Greenblatt et al.[16]

Table 2. Indolent CD8-positive lymphoid proliferation of acral sites

	CD3	CD8	CD4	CD2	CD5	CD7	CD20	CD30	CD56	TIA-1	Granzyme B	Perforin	EBER	Ki-67
Vaillant et al.[2]	+	+	–	–	+	–	ND	ND	ND	ND	ND	ND	ND	<5%
Friedmann et al.[3]	+	50–75%	<25%	ND	+	–	<25%	–	ND	ND	ND	ND	ND	ND
Eich et al.[20]	ND	+	ND	ND	ND	ND	ND	–	ND	ND	ND	ND	ND	ND
Khamaysi et al.[21]	+	+	–	ND	ND	+	–	–	–	+	ND	ND	ND	5–10%
Fika et al.[22]	+	+	–	ND	ND	ND	ND	–	–	+	ND	ND	ND	ND
Petrella et al.[1]														
1	+	+	–	–	+	ND	–	–	–	+	–	ND	–	<10%
2	+	+	–	+	+	ND	–	–	–	+	–	ND	–	<10%
3	+	+	–	+	+	ND	–	–	–	+	–	ND	–	<10%
4	+	+	–	+	–	ND	–	–	–	+	–	ND	–	<10%
Li et al.[4]	+	+	–	+	+	–	–	–	–	+	–	ND	–	5%
Beltraminelli et al.[5]														
1	+	+	–	ND	+	ND	ND	–	–	+	ND	ND	–	5–20%
2	+	+	–	ND	+	ND	ND	–	–	+	ND	ND	–	5–20%
3	+	+	–	ND	+	ND	ND	–	–	ND	ND	ND	–	5–20%
Suchak et al.[6]														
1	+/–	+	–	ND	+/–	+/–	ND	–	–	+	+	ND	–	<10%
2	ND	+	–	ND	ND	–	ND	–	–	+	ND	ND	–	ND
Ryan et al.[7]	+	+	–	–	+	–	ND	–	–	–	–	ND	–	10%
Swick et al.[8]														
1	+	+	–	ND	ND	ND	–	–	–	ND	ND	ND	–	<10%
2	+	+	–	ND	ND	ND	ND	–	–	ND	ND	ND	ND	ND
Geraud et al.[9]	+	+	–	ND	+		–	–	ND	–	ND	–	ND	5–10%
Zeng et al.[10]														
1	+	+	–	ND	+	–	–	–	–	+	–	+	–	<25%
2	+	+	–	ND	+	–	–	+ (focal)	–	–	–	ND	–	90%
Butsch et al.[11]	+	+	–	ND	ND	ND	–	–	–	ND	ND	ND	ND	10%
Valois et al.[12]	+	+	–	ND	+	ND	ND	–	–	+	ND	ND	ND	20%
Milley et al.[13]	ND	+	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Wobser et al.[14]	+	+	–	+	+	–	–	–	–	+	–	–	–	<10%
Kempf[15]														
1	+	80%	30%	+	+	ND	ND	–	–	+	+	–	–	ND
2	+	80%	30%	+	+	+	ND	–	–	+	+	–	–	ND
3	–	90%	10%	ND	+	ND	ND	–	–	ND	ND	ND	–	ND
Greenblatt et al.[16]														
1*	+	+	–	+	+	+	<5%	–	–	+	–	ND	–	40%
2	+	+	–	–	+	–	–	–	–	+	–	ND	–	10%
3	+	+	–	+	–	+	<5%	–	–	+	ND	ND	–	10%
4	+	+	–	–	+	–	ND	–	–	+	20%	ND	–	30%
5	+	+	+	+	+	+	<5%	–	–	+	–	ND	–	10%
6	+	+	+	+	+	+	–	–	–	+	10%	ND	–	40%
Hagen et al.[17] 1	+	+	+ (minority of cells)	ND	20%	20%	<15%	ND	ND	+	ND	ND	ND	ND
2	+	+	+	ND	80%	50%	NQ	–	–	+	+	ND	ND	ND
Wobser et al.[18] 1	+	+	–	ND	+	+	ND	ND	ND	+	+	–	ND	20%
2	+	+	–	+	+	+	ND	ND	ND	+	–	+	ND	10-20%
3	+	+	–	+	+	+	ND	ND	ND	+	–	–	ND	20%
4	+	+	–	+	+	+	ND	ND	ND	+	–	+	ND	10-20%
5	+	+	–	+	+	+	ND	ND	ND	+	–	+	ND	5%
Li et al.[19]	+	+	–	+	+	+	–	–	ND	50%	–	ND	–	15%
	+	+	–	+	+	+	–	–	–	+	–	ND	–	10%
	+	+	+	+	+	+	–	–	ND	ND	ND	ND	ND	ND
	+	+	–	+	–	ND	Few	–	–	90%	ND	ND	ND	10%
	+	+	–	ND	–	–	–	–	–	40%	–	ND	–	ND
	+	+	–	ND	+	+	Few	–	–	20%	–	ND	–	ND
	+	+	–	+	+	+	–	–	–	50%	–	ND	–	15%
Kluk et al., 2014 (this series)														
1	ND	+	ND	ND	ND	ND	ND	–	ND	+	–	ND	ND	10%
2	ND	+	ND	+/–	+/–	ND	ND	–	–	+	–	+	–	10–20%
3	ND	+	ND	ND	ND	ND	ND	ND	–	+	–	+	–	40%
4*	ND	+	ND	–	–	ND	ND	ND	ND	–	–	ND	ND	20–30%

EBER, Epstein–Barr virus-encoded RNA; ND, not done or not specified; NQ, not quantified.
Immunocytochemical characteristics of cases reported to date.
*Update on a case previously reported by Greenblatt et al.[16]

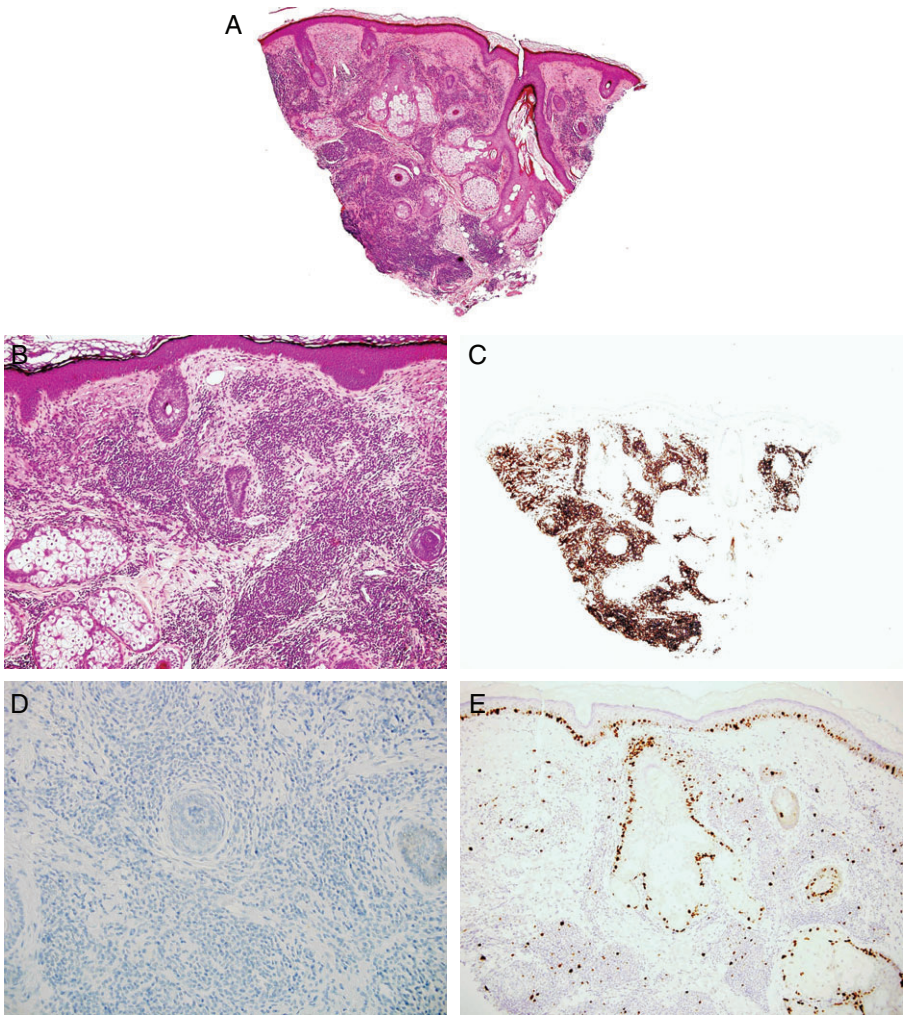

Fig. 1. A) A dense nonepidermotropic mononuclear cell infiltrate (H&E, ×10). (B) (Case 1) Indolent CD8-positive lymphoid proliferation. The infiltrate has a perivascular accentuation & is dense and monotonous (H&E, ×20). (C) (Case 1) Indolent CD8-positive lymphoid proliferation. The neoplastic cells are uniformly strongly CD8+ (×10). (D) (Case 1) Indolent CD8-positive lymphoid proliferation. Immunohistochemistry for PD-1 is uniformly negative (×40). (E) (Case 1) Indolent CD8-positive lymphoid proliferation. There is a very low proliferation fraction with Ki-67, approximately 10% (×20).

declined treatment with radiotherapy and remains systemically well with persistent papules on his left ear 21 months later.

Case 4

A 47-year-old female presented in 2010 with a 14-month history of an asymptomatic 10 mm nodule on the nasal tip and several 3–4 mm pink papules on the dorsal right hand. She was otherwise well with no history of skin disease, malignancy or immunosuppression and no B symptoms, lymphadenopathy or hepatosplenomegaly. This case has been previously reported in Ref. 16.

A skin biopsy taken from a representative papule on her right hand showed the characteristic features of indolent CD8-positive lymphoid proliferation, as previously described, however TCR gene rearrangement studies failed to amplify.[16] Staging investigations including computerized tomography and a bone marrow examination were normal or negative.

Biopsies taken from different sites showed the same histopathologic features and the lesions were, therefore, felt to represent the same disease process. In view of the atypical presentation with multiple lesions, the nasal lesion was treated with electron beam radiotherapy and the papules on her hand were treated with superficial radiotherapy to a dose of 30Gy in 15 fractions leading to complete resolution. Although she has remained well with no evidence of systemic disease progression since her initial diagnosis, she has continued to develop new and recurrent papules on her hands, feet, thighs and nose. She

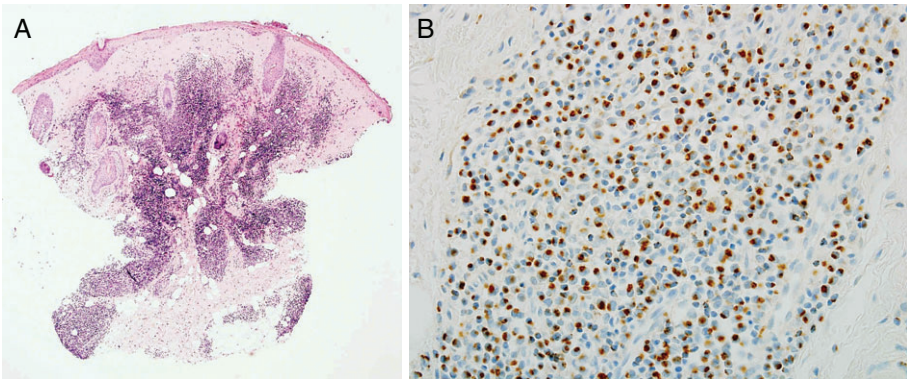

Fig. 2. A) A dense nonepidermotropic mononuclear cell infiltrate, which extends into the subcutis (H&E, ×10). (B) (Case 2) Indolent CD8-positive lymphoid proliferation. There is diffuse expression of TIA-1 (×100).

received further radiotherapy to a dose of 30Gy in 15 fractions to lesions on her left thumb, left dorsal hand, right ankle, left ankle and right foot in November 2010. A complete resolution was observed at each of these sites. Given the excellent response, subsequent lesions on the right thigh, right hand, right lateral foot, left hand and left side of the nose were treated with lower doses of radiotherapy, such as those typically used in mycosis fungoides i.e. 12Gy in three fractions, with complete response in all sites treated except for a single lesion on the dorsum of her left hand.

In 2013, a diagnostic excision of the persistent lesion on the dorsum of her left hand (Fig. 4A) showed a largely perivascular monotonous mononuclear cell infiltrate with focal involvement of the epidermis and an interstitial component (Fig. 4B,C). The cells were small to medium in size and morphologically varied in cytology from lymphocytoid to monocytoid with occasional lymphoblast-like cells (Fig. 4D). There was mild, although definite, cytological atypia; most cells had enlarged nuclei, a fine chromatin pattern & often folded nuclear contours. Nucleoli were largely inconspicuous. Immunocytochemistry confirmed a CD8(+) T-cell phenotype (Fig. 4E,F) with loss of both CD2 (Fig. 4G) and CD5. CD4 was negative. CD56 was negative, and TIA-1 and Granzyme B were negative in the vast majority of cells. Similarly, the majority did not express either CD45 RA or RO. Ki67 confirmed a moderate proliferation fraction (approximately 20–30%). TCR gene analysis on this biopsy and further specimens at later dates and different sites confirmed the same monoclonal rearrangement.

In view of the multifocal and recurrent pattern of cutaneous involvement in this patient, alpha interferon 3MU 3× weekly was initiated in April 2013. Despite an initial improvement with partial regression of existing papules, interferon was recently stopped because of intolerable side effects and she continues to develop new skin lesions. The patient remains under observation and further low dose radiotherapy to individual lesions or systemic treatment e.g. methotrexate may be considered. Although the disease appears to be following a benign course, management of this recurrent atypical cytotoxic clonal infiltrate is without precedent and there is uncertainty about the long-term outlook.

Discussion

Including this series, there have been 51 cases of indolent CD8-positive lymphoid proliferation reported to date[1–22] (Table 1). The term was originally used to describe four patients with slowly progressive nodules or plaques confined to one or both ears, characterized by a nonepidermotropic infiltrate of monomorphous blast-like T-cells in the dermis with a CD3(+) CD4(−) CD8(+) CD30(−) TIA-1(+) Granzyme B(−) BF-1 (+) CD56(−) immunophenotype, a low proliferation fraction and the presence of clonal T-cell receptor (TCR) gene rearrangements in three out of four cases. Despite the pathologic findings and immunophenotype of a cytotoxic high-grade lymphoma, staging investigations failed to identify extracutaneous disease in these patients and an indolent clinical course was observed in each case whether treated by surgery, radiotherapy or even simple observation.[1] The intermittent symptoms reported in patients with similar cytotoxic proliferations of the gastrointestinal tract suggest a comparably protracted clinical course, with absent disease progression and no deaths for the duration of the reported follow-up period.[23–26]

Affected individuals are mostly older than 50 years (mean age 56 years) and a slight male

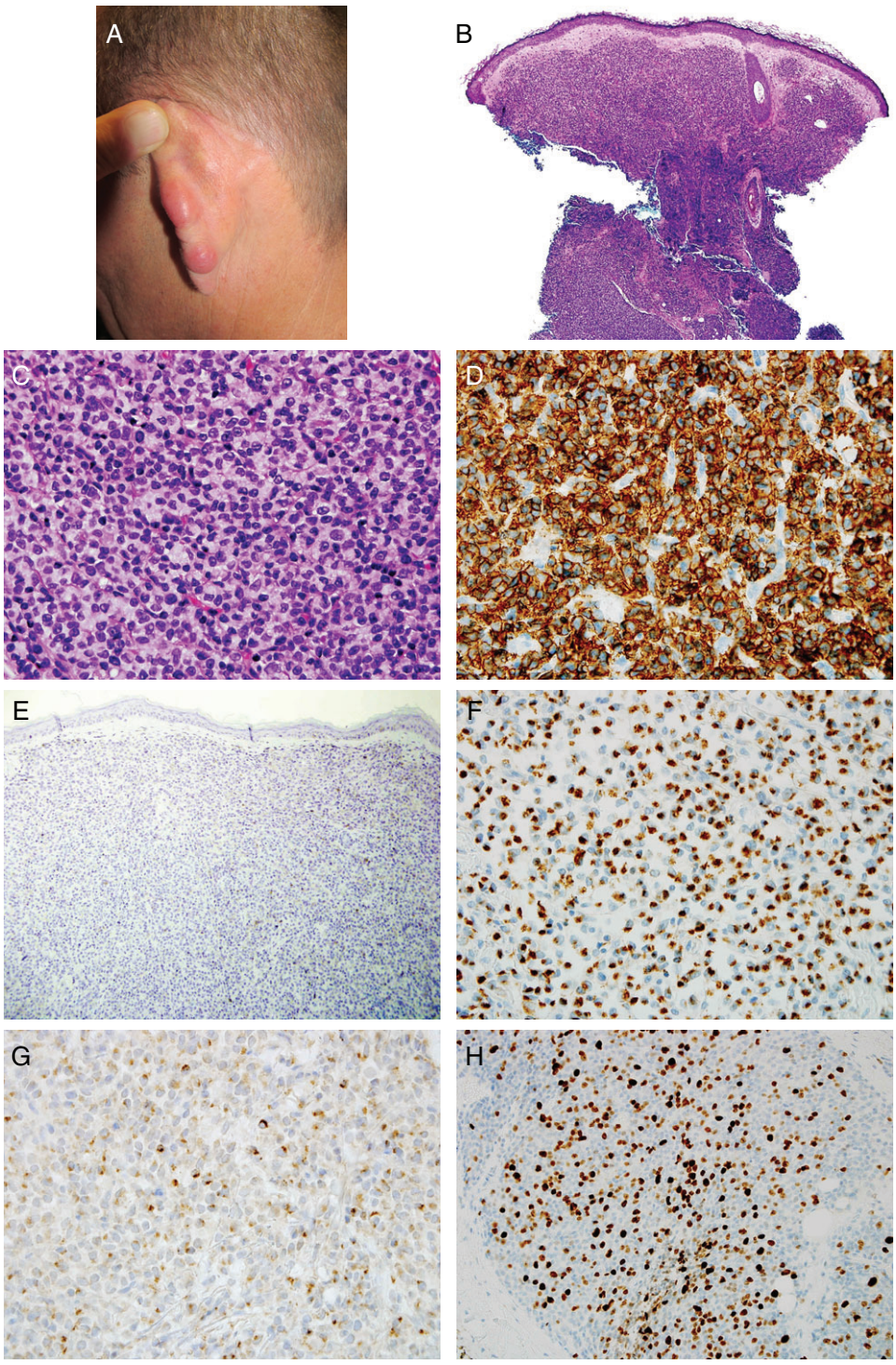

Fig. 3. A) Erythematous papules and nodules on the helix of the left ear. (B) (Case 3) Indolent CD8-positive lymphoid proliferation. A dense monotonous infiltrate is present throughout the dermis, with a striking grenz zone (H&E, ×10). (C) (Case 3) Indolent CD8-positive lymphoid proliferation. The infiltrate consists of a uniform population of atypical lymphocytes (H&E, ×200). (D) (Case 3) Indolent CD8-positive lymphoid proliferation. There is strong expression of CD8 by all the neoplastic cells (×200). (E) (Case 3) Indolent CD8-positive lymphoid proliferation. The infiltrate does not express CD4 (×200). (F) (Case 3) Indolent CD8-positive lymphoid proliferation. All cells expressed TIA-1 (×20). (G) (Case 3) Indolent CD8-positive lymphoid proliferation. A significant proportion of the infiltrate, although not all, was positive for perforin (×100). (H) (Case 3) Indolent CD8-positive lymphoid proliferation. Ki-67 revealed a moderately high proliferation fraction, approximately 40% (×100).

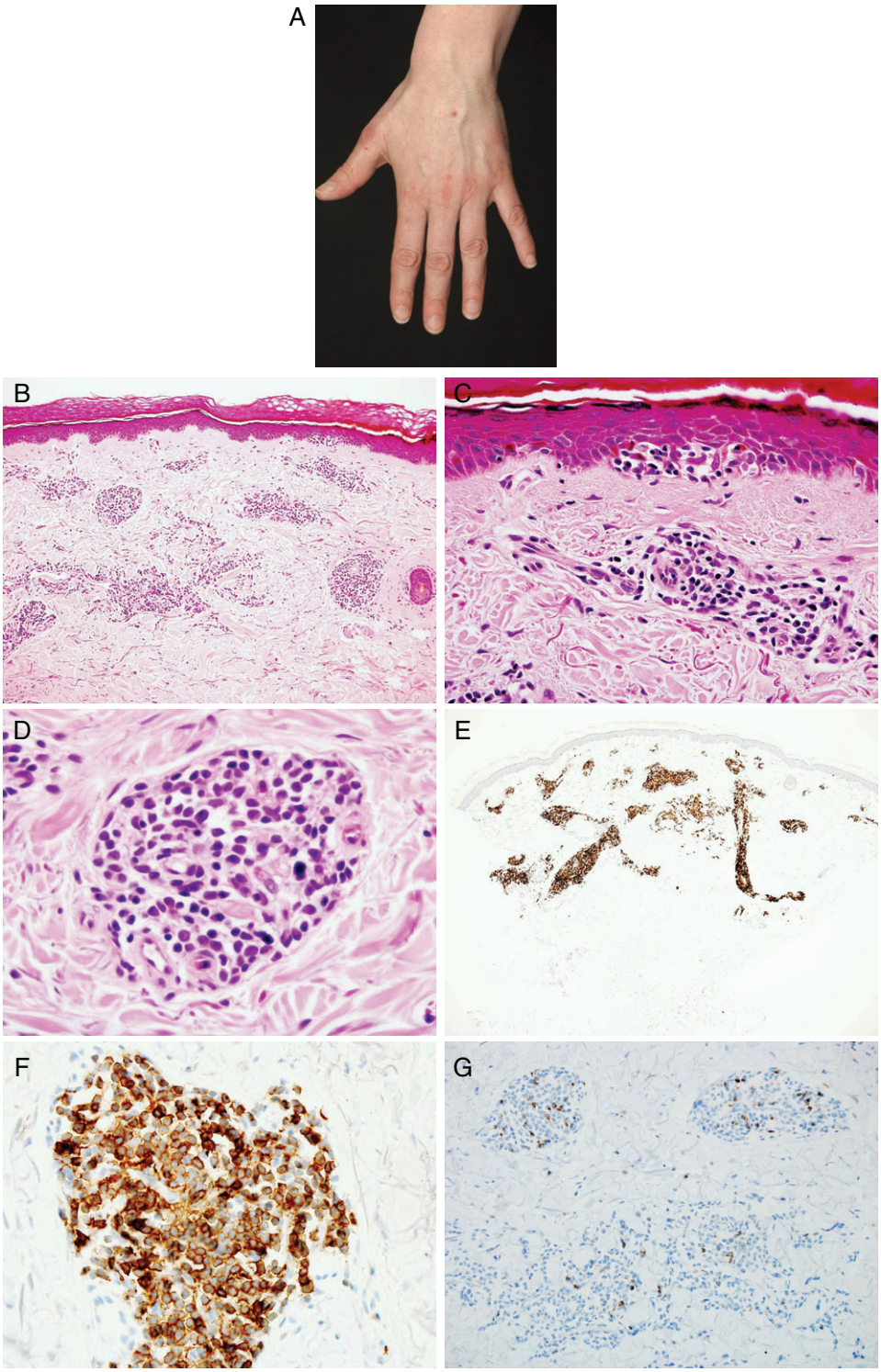

Fig. 4. A) A persistent papule on the dorsum of the left hand. (B) (Case 4) Indolent CD8-positive lymphoid proliferation. The infiltrate is predominantly perivascular, but also interstitial and has focal epidermal involvement (H&E, ×20). (C) (Case 4) Indolent CD8-positive lymphoid proliferation. Focal Pautrier micro-abscess formation (H&E, ×100). (D) (Case 4) Indolent CD8-positive lymphoid proliferation. The cells are lymphoid, hyperchromatic and mild pleomorphic (H&E, ×200). (E) (Case 4) Indolent CD8-positive lymphoid proliferation. There is diffuse and strong expression of CD8 (×10). (F) (Case 4) Indolent CD8-positive lymphoid proliferation. There is diffuse and strong expression of CD8 (×200). (G) (Case 4) Indolent CD8-positive lymphoid proliferation. There is loss of CD2 by most cells (×40).

predominance has been observed (M:F 1.7:1). Although the majority of cases (28/51 = 55%) arise on the ear, it is now recognized that lesions may occur at other locations, particularly on the nose,[6,7,13,16,19] and on the hands and feet,[14,16,18,21] suggesting that a local antigenic stimulus specific to the ear is unlikely.[14] The indolent nature of the process, and innocuous clinical appearance, might lead to a consideration of a reactive rather than lymphomatous process, however the monotonous and cytologically atypical infiltrate, the abnormal loss of T-cell associated antigens, and clonality, militate against this interpretation.

By and large, lesions are solitary at presentation, however bilateral symmetrical disease has been described in at least seven patients.[1,5,8,11,14,18] Whilst limited cutaneous relapses may occur,[1,2,10,15,16,19] there have been no examples of progression to systemic disease or disease-related deaths over follow-up periods ranging from 3 to 168 months from diagnosis regardless of whether patients were treated with topical corticosteroids, radiotherapy, surgical excision or observed without any specific intervention (Tables 1 and 2). Multifocal cutaneous disease has only been reported in four cases to date[3,15,16,18] and appears to be associated with a similarly benign clinical course. Interferon, psoralen-ultraviolet A phototherapy (PUVA) and methotrexate have been initiated in these patients in an attempt to reduce the frequency of cutaneous relapses with variable success.[3,15] Case 4 in this series is currently unique. The continued appearance of lesions at a variety of sites is intriguing. No history of allergy, contact reactions, occupational details or other features exists to offer a hypothesis for the repeated development of papules.

While histopathological descriptions are fairly consistent, variability in epidermal involvement and proliferation index have been described, but with similar clinical outcomes (Tables 1 and 2).[2,4,10,11,14,16] The lack of pre-existing patches or plaques, absence of CD30 expression and lack of preferential involvement of the subcutis distinguishes these cases from other subtypes of cutaneous T-cell lymphoma with CD8 expression including occasional examples of mycosis fungoides and CD30-positive cutaneous lymphoproliferative disorders, 50% of cases of pagetoid reticulosis and almost all cases of subcutaneous panniculitis-like T-cell lymphoma.[1,6,8,10,15] The absence of EBV and CD56 expression excludes extranodal NK/T-cell lymphoma, nasal type and the benign clinical course, usually nonepidermotropic CD8(+) lymphoid infiltrate and absence of angiocentricity and angiodestruction exclude primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma.[6,10,15]

Collectively, the cases of primary cutaneous indolent CD8-positive T-cell lymphoid proliferation described to date indicate a distinct and reproducible entity that tends to arise in peripheral locations including the nose and at acral sites, but with a predilection for the ear that is as yet unexplained. They do not, however, correspond to any of the well-defined subtypes of cutaneous T-cell lymphoma delineated in the World Health Organisation (WHO) – European Organisation for Research and Treatment of Cancer (EORTC) Classification of Cutaneous Lymphomas of 2005,[27] nor the 2008 WHO Classification of Tumours of Hematopoietic and Lymphoid Tissue[28] and, as such, may be labeled as peripheral T-cell lymphoma, NOS (PTL, NOS) according to current classification schemes. Indeed, a number of cases in the senior author's experience were so classified. CD8 expression has been observed in 15% of PTL, NOS presenting in the skin and is associated with a poor prognosis and a median survival of 28 months.[15] Designation of cases of indolent CD8-positive lymphoid proliferation as PTL, NOS may lead to the use of unnecessarily aggressive therapies with attendant morbidity, possibly mortality. Hitherto, specific and reliable markers to differentiate this entity from other CD8(+) lymphomas have not been identified, however Wobser and colleagues recently showed co-labeling with CD8 and CD68 in five out of five cases of indolent CD8-positive lymphoid proliferation compared with 0 out of 39 cases of other CD8(+) lymphomas. Based on their observations, they have recommended CD68 as a new discriminative marker to help distinguish indolent CD8-positive lymphoid proliferation from other CD8(+) cutaneous lymphomas in ambiguous cases.[18]

Some caution is advised, however. Although the cases of indolent CD8-positive lymphoid proliferation described thus far appear to follow the same benign clinical course, the long-term outlook for these patients, particularly those with recurrent cutaneous disease or multifocal presentations, is yet to be determined e.g. Case 2 in this series has only completed 11 months of follow-up at the time of publication. Dermatologists should therefore remain guarded about the prognosis and full staging and longitudinal

observation are recommended until more is understood about the condition.

Indolent CD8-positive lymphoid proliferation is a distinctive and readily identifiable entity. The authors recommend that it is included as such in the future consensus revision of cutaneous lymphoma classification.

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