


Primary cutaneous acral CD8+ T-cell lymphomas relapse more frequently in younger patients

Primary cutaneous acral CD8+ T-cell lymphoma (PCA-CD8+ TCL), originally named indolent primary cutaneous CD8+ T-cell lymphoproliferation, is a rare entity that was classified as “provisional” in the recently revised World Health Organization (WHO) classification of haematopoietic and lymphoid tissue tumours (Swerdlow et al, 2016). PCA-CD8+ TCL usually has a favourable prognosis.

Except for one reported case with extracutaneous involvement (Alberti-Violetti et al, 2017), only cutaneous relapses have been described. However, these relapses have not yet been clinically characterized.

Herein, we update a case of PCA-CD8+ TCL, with a very late relapse, that had originally been reported by Petrella et al (2007). We analysed the literature and compared clinical characteristics of patients with relapsing and non-relapsing disease.

In July 2006, a 29-year-old woman with no remarkable medical history was referred for a painless nodule on the left ear helix of 4 months duration (Fig 1A). Histological examination of the surgically excised lesion found a dense and diffuse proliferation of monomorphic, medium-sized T cells throughout the dermis and subcutis. The tumour-cell immunophenotype was CD3+CD8+CD4–TIA1+granzyme B–CD2–CD5–CD7–CD30–CD56–CD99+ and Ki67 < 10%. T-cell receptor gene analysis showed monoclonal rearrangement. Staging, including computed-tomography (CT) scan, bone marrow biopsy and complete blood count, was normal. No circulating T-cell clone was found. Borrelia burgdorferi serology was negative. Radiotherapy was delivered, obtaining a complete response.

Seven years later she was referred again for 2 slowly enlarging, poorly defined papules on the right ear helix (Fig 1B). No enlarged lymph nodes were found during physical examination. Positron-emission tomography–CT scan and peripheral blood tests, including complete blood count and T-cell clonality, were normal or negative. Papule histological features were very similar to those of the initial lesion, except for the deeper location of the cellular proliferation, resulting in a thicker Grenz zone. Radiotherapy was again delivered, followed several weeks later by complete remission. After three more years of follow-up, no recurrence has occurred.

Since the initial description of this entity by Petrella et al (2007), 54 PCA-CD8+ TCL cases have been published, predominantly involving the ear (n = 31). Recurrences/progression occurred in 11 (20%) of these cases, including our patient and 5 others involving the ear. Characteristics at initial diagnosis and relapse/progression of these 8 men and 3 women, median age 47 (range: 29–69) years at diagnosis, are detailed in Table I.

Initially, all relapsing patients’ lesions were papules or nodules, except one with multiple lesions who also had plaques. At onset, three of the 11 patients had at least 2
non-contiguous body regions involved and were classified as T3; 6 had ear involvement; none had systemic involvement. The median time to diagnosis was 11 months (range: 4 months to 35 years). Reported initial treatments were: 2 watch-and-wait, 2 surgical excisions, 3 radiotherapy, 3 underwent surgical excision and radiotherapy.

Ten patients relapsed and another had only slow progression with median follow-up at 117 (range: 0–168) months. Recurrences/progression occurred on acral, non-acral sites or both in 7, 2 and 2 patients, respectively. Median progression-free survival was 12 months (range: 9–92 months). Staging showed local extracutaneous involvement of the bony nasal septum in one patient. According to the Tumour, Node and Metastasis (TNM) system (Appendix S1), relapse/progression maximum T staging was: rT1 (solitary skin involvement)/rT2 (multiple lesions limited to 1 body region or 2 contiguous body regions) for 6 (55%) patients and rT3 (generalized skin lesions with 2 non-contiguous body regions or ≥3 body regions involved) for 5 (45%). Five of the 6 rT1/T2 patients only relapsed once and none progressed. They underwent local surgery or radiotherapy or received no treatment; 4 of them achieved complete responses. In contrast, all 5 rT3 patients suffered several relapses/progression; 3 of them received systemic treatments; 2 are disease-free. All 11 patients were alive at last update.

Relapsing/progressing patients were younger than non-relapsers (47 vs. 56 years, respectively; \( P = 0.048 \)) but were comparable for sex and tumour location (ear vs. other acral sites) \( (P > 0.4) \) (Mann–Whitney test). Follow-up was shorter for patients without relapse/progression than those who relapsed/progressed (mean: 14 vs. 42 months; \( P = 0.03 \)).

Our analysis of published PCA-CD8+ TCL cases revealed a 20% relapse/progression rate with no distant extracutaneous dissemination, and no disease-related death, although this

Fig 1. Clinical and histopathological characteristics of PCA-CD8+ TCL on the ear at diagnosis and relapse. (A) Initial clinical examination showed a solitary 2.0-cm, red, ovoid, poorly defined soft nodule on the left ear. Histology of the surgically excised lesion revealed a mononuclear cell infiltrate composed of medium-sized lymphoid cells extending into the subcutis, without epidermotropism. A Grenz zone (white asterisk) was present. The tumour cells had irregular, blast-like nuclei with small nucleoli and clear chromatin. Immunohistochemistry showed medium-sized lymphocytes strongly expressing CD3 and CD8, but not CD4, and were positive for T-cell intracytoplasmic antigen-1 (TIA1). (B) At relapse, 2 papules (white arrows) had appeared on the right ear. Their histopathological findings were similar to those of the initial lesion, except for their thicker Grenz zone (white asterisks).
## Table I. Clinical features of patients with primary cutaneous acral CD8+ T-cell lymphoma relapses (literature review).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (years)/sex</th>
<th>Time to diagnosis (months)</th>
<th>Initial findings</th>
<th>Relapse/progression (time since diagnosis)</th>
<th>Last up-date (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaillant et al (1993)</td>
<td>45/M</td>
<td>Unknown</td>
<td>R shoulder, nodule, 20 mm; T1a, W+W, PD</td>
<td><strong>Progression (24 months)</strong>: R shoulder, nodule, NR; rT2, W+W, PD <strong>Progression (9 months)</strong>: L ear, nodule, 20 mm; rT1a, W+W, SD</td>
<td>AWD, 132</td>
</tr>
<tr>
<td>Petrella et al (2007)</td>
<td>61/M</td>
<td>9</td>
<td>R ear, nodule, 30 mm; T1a, RT, CR</td>
<td><strong>Progression (12 months)</strong>: R and L ears, nodule, NR; rT3a, surgical excision, PR <strong>Progression (24 months)</strong>: R ear, nodule, NR; rT1a, surgical excision, CR</td>
<td>AWD, 12</td>
</tr>
<tr>
<td></td>
<td>47/M</td>
<td>4</td>
<td>R and L ears, nodule, 15 mm; T3a, W+W, PR</td>
<td><strong>Progression (30 months)</strong>: R ear, nodule, NR; rT1a, surgical excision, CR <strong>Relapse (24 months)</strong>: L ear, NR, NR; rT1a, RT, regression</td>
<td>AWD, 156</td>
</tr>
<tr>
<td>Zeng et al (2012)</td>
<td>38/M</td>
<td>6</td>
<td>L ear, nodule, 15 mm; T1a, surgical excision, CR</td>
<td><strong>Relapse (34 months)</strong>: L foot and toes, plaques; rT1a, RT, CR <strong>Relapse (45 months)</strong>: L foot, 1 plaque, NR; rT2a, RT, CR</td>
<td>AWD, 0</td>
</tr>
<tr>
<td>Kempf et al (2013)</td>
<td>48/M</td>
<td>Unknown</td>
<td>R buttock, nodule, 10 mm; T1a, surgical excision, CR</td>
<td><strong>Relapse (48 months)</strong>: L foot (papules) and R ear (3 papulonodules), 8 mm; rT3a, RT and MTX, CR</td>
<td>AWD, 55</td>
</tr>
<tr>
<td>Wobser et al (2015)</td>
<td>59/M</td>
<td>Unknown</td>
<td>Ear, papule, &lt;10 mm; T1a, surgical excision and RT, CR</td>
<td><strong>Relapse (12 months)</strong>: R ear, papule, NR; rT1a, surgical excision or RT, CR <strong>Relapse (36 months)</strong>: L ear, papule, NR; rT1a, surgical excision or RT, CR</td>
<td>AWD, 117</td>
</tr>
<tr>
<td>Li et al (2014)</td>
<td>41/F</td>
<td>36</td>
<td>L nose; NR, NR; T1, RT, CR</td>
<td><strong>Relapse (60 months)</strong>: nose, papule, NR; rT1a, surgical excision or RT, CR <strong>Relapse (NR)</strong>: R wing and R dorsal nose, R helix; rT2a, RT, CR <strong>Relapse (&lt;12 months)</strong>: hands, feet, thigh and nose, papules; rT3b, RT, PR</td>
<td>AWD, 134</td>
</tr>
<tr>
<td>Kluk et al (2016)</td>
<td>47/F</td>
<td>14</td>
<td>Nose and R hand, papules and 1 nodule, 10 mm; T3a, RT, CR</td>
<td><strong>Relapse (NR)</strong>: R upper back, NR; rT1, NR, CR <strong>Progression (36 months)</strong>: multiple sites, NR, NR; IFN, PD</td>
<td>AWD, 36</td>
</tr>
<tr>
<td>Virmani et al (2016)</td>
<td>45/M</td>
<td>Unknown</td>
<td>Eyelid, NR, NR; T1a, NR, NR</td>
<td><strong>Relapse (NR)</strong>: R ear, papule, NR; rT1a, surgical excision or RT, CR</td>
<td>AWD, 0</td>
</tr>
<tr>
<td>Alberti-Violetti et al (2017)</td>
<td>69/M</td>
<td>420 (L ear) several prior relapses</td>
<td>Thighs, buttocks, feet, ears; plaques, nodules and 1 papule; NR; rT3b, surgical excision (ear) and RT (thighs, buttocks), PR</td>
<td><strong>Progression (12 months)</strong>: nose (mass), hands and legs (nodules); NR; rT3b, gemcitabine, bendamustine, gemcitabine + oxaliplatin, SD</td>
<td>AWD, 36</td>
</tr>
<tr>
<td>This case (Petrella et al, 2007)</td>
<td>29/F</td>
<td>4</td>
<td>L ear, nodule, 20 mm; T1a, surgical excision +RT, CR</td>
<td><strong>Relapse (92 months)</strong>: R ear, 2 papules, 6 mm; rT2a, RT, CR</td>
<td>AWD, 129</td>
</tr>
</tbody>
</table>

AWD, alive with disease; AWOD, alive without disease; CR, complete response; F, female; IFN, interferon; L, left; M, male; MTX, low-dose methotrexate; NR, not reported; PD, progressive disease; PR, partial response; R, right; RT, radiation therapy; SD, stable disease; W+W, watch and wait.

*See Appendix S1 for details.
frequency might be underestimated because the follow-up of non-relapsing patients was shorter than that of those who relapsed. PCA-CD8+ TCL relapses/progression should be systematically recorded in available databases to better determine their frequency and characteristics. In routine practice, even though PCA-CD8+ TCL is indolent in most cases, regular monitoring should be implemented to detect potentially late recurrence.

Our results indicating that relapsing patients may be younger require further confirmation with a larger cohort. Whether recurrence and primary lesions share the same genotype remains to be determined with molecular studies.

Finally, based on our analysis, 2 patient groups may be defined according to their maximum T stages at relapse/progression: one group, with either solitary or 1 or 2 contiguous body region recurrence(s), follows an indolent course requiring local treatment; the other group, with at least 1 relapse involving 2 non-contiguous or ≥3 body regions, experienced repeated relapses that led to chronic disease requiring systemic therapy for 27% of them. These findings confirm the indolent course of PCA-CD8+ TCLs associated with favourable prognoses without death. However, these TCLs might be heterogeneous regarding potentially late and multiple relapses, sometimes requiring systemic therapy.

Authors contribution

EM designed the study. EM, EMar, LL, AM, FG and TP wrote the paper. AM, LL and TP analysed the data. EMar, FG and TP performed the research.

Conflict of Interest

The authors reported no potential conflicts of interest.

References


