

## SHORT COMMUNICATION

Primary Cutaneous CD8<sup>+</sup> T-cell Lymphoma Masquerading as Acral Vascular Syndrome

Francois Le Loarer<sup>1,7</sup>, Stéphane Barette<sup>2</sup>, Laurent Vallat<sup>3</sup>, Delphine Carre<sup>1</sup>, Rachid El Amarti<sup>4</sup>, Carlos A. Torres-Cabala<sup>5</sup>, Patrice Cacoub<sup>6</sup>, Damien Sene<sup>6</sup>, Philippe Courville<sup>7</sup> and Pierre Bravard<sup>1</sup>

Departments of <sup>1</sup>Dermatology and <sup>4</sup>Oncology, GHJ Jacques Monod Hospital, 29 Avenue Pierre Mendès, FR-76290 Montivilliers, Le Havre, Departments of <sup>2</sup>Dermatology, <sup>6</sup>Internal Medicine, and <sup>3</sup>Haematological Biology, Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique Hôpitaux de Paris et Université Pierre et Marie Curie, Paris, France, <sup>5</sup>Department of Pathology, University of Texas, MD Anderson Cancer Center, Houston, TX, USA and Service d'Anatomie Pathologique, <sup>7</sup>Service d'Anatomie Pathologique, Rouen University Hospital, Rouen, France. E-mail: leloafra@gmail.com  
Accepted Apr 15, 2013; Epub ahead of print Aug 27, 2013

Acral vascular syndromes (AVS) require thorough testing as, they can reveal varied underlying conditions, including immunological and haematological disorders or neoplasia (1). We report here the first case of primary cutaneous CD8<sup>+</sup> T-cell lymphoma (CTCL) presenting with ulcerated infiltrated patches exclusively located on acral areas including fingers, toes, ears and nose. This case which evolved over 4 years, raises challenging questions as to how it should be classified and as to whether it may impact our current diagnostic approach to AVS.

## CASE REPORT

A 74-year-old man was hospitalized to investigate ulcerated AVS. He had developed permanent and painful erythematous

patches on his fingers and toes 5 months earlier. His condition had worsened in early summer, with onset of ulcerations on distal portions of his fingers and toes, along with extension to his ears and nose without systemic symptoms. The patient had emigrated from Algeria 40 years previously, and had formerly worked in a car factory. Medical records included pulmonary tuberculosis 30 years previously, uncomplicated type 2 diabetes controlled with metformin, uncomplicated chronic hepatitis B and delta, and a 40 pack-year history of cigarette smoking. Physical examination revealed erythematous ulcerated patches on the dorso-lateral aspects of all his fingers and toes, ears and nose (Fig. 1A–C). No livedo or cyanosis were found.

Laboratory tests showed normal liver and kidney functions, erythrocyte sedimentation rate, reactive protein C, serum complement levels blood count, and coagulation tests. Serological tests were all negative for rheumatoid factor, antinuclear antibodies, anticardiolipin antibodies, HIV and hepatitis C virus, while chronic co-infection with hepatitis B and Delta viruses without viral replication was confirmed. Brachial arteriography and muscular biopsy were within normal ranges. Tests for cold agglutinins, cryoglobulin, and cryofibrinogen were repeatedly negative. Computed tomography of the thorax, abdomen and pelvis revealed only a thyroid multi-nodular goitre, along with biological hyperthyroidism without anti-TSH receptor, thyroglobulin or anti-thyroperoxidase antibodies. The attending hepatologist introduced an antiviral therapy in this setting of chronic B hepatitis (adefovir dipivoxil, 10 mg/day) and the patient stopped smoking, without subsequent improvement.

On re-examination, biopsies were performed on infiltrated patches peripheral to the ulcerations of toes and fingers, and corticosteroid regimen was started. On histopathological analysis, the lower dermis was found to be massively infiltrated by medium- to large-sized pleomorphic lymphocytes sparing the epidermis and subcutis. Focal features of angiocentrism and angiodestruction were noticed on a small vessel of lower dermis (Fig. S1<sup>1</sup>). Atypical cells were diffusely positive for CD3, CD8, beta F1, focally positive for program death 1, and negative for CD4, CD5, T-cell receptor (TCR) gamma, CD20, CD30, CD56, CD21, CXCL13. TIA-1 and granzyme B were strongly expressed. Staining for Epstein-Barr virus was negative by *in situ* hybridization (Epstein-Barr encoding region). The proliferation index, as measured by Ki-67, was 40% (Fig. S2<sup>1</sup>).

These findings were consistent with a T-cell lymphoma with CD8<sup>+</sup> cytotoxic phenotype.



Fig. 1. Cutaneous lymphoma masquerading as acral syndrome. (a–c) Clinical features at initial presentation and after necrosis onset (d, e). Ulcerated infiltrated patches were symmetrically distributed to: (a) dorso-lateral aspects of all fingers, (b, c) tips of toes (not shown). Evolution was marred with necrosis of lesions as illustrated on hands and toes (d, e) after detersion phase.

<sup>1</sup><https://doi.org/10.2340/00015555-1670>

Clonal studies identified a monoclonal rearrangement of TCR-gamma chain on biopsy specimens without concomitant delta gene rearrangement. No circulating clone was detected for TCR or for immunoglobulin heavy-chain receptor genes. Staging evaluation was negative for systemic involvement, including bone marrow aspiration and biopsy. LDH level and serum electrophoresis were within normal range. Positron emission tomography (PET) showed hypermetabolic uptake restricted to acral areas.

Given his history of chronic viral hepatitis, the patient was referred to a reference centre for chronic viral hepatitis and cryoglobulinaemia. The tests were repeated there, including skin biopsies, and the results corroborated the initial findings. Notably, all biopsies performed on lesional sites proved histologically to be neoplastic, including the toes, fingers and ears.

As patient's condition worsened, with necrotizing ulcerations of the lesions along with increasing pain (Fig. 1 D–E), an interferon regimen was introduced (interferon alpha-2A 3 million units, 3 times a week), but this did not alter the course of the disease after 3 months. Therefore, 6 cycles of CHOP (cyclophosphamide, vincristine, cytarabine and dexamethasone) were undertaken, which elicited a complete response, but relapse occurred within one month. Gemcitabine was introduced, but not tolerated. Meanwhile, the patient underwent thyroid surgical resection to manage hyperthyroidism unresponsive to medical treatment. Histological examination highlighted multiple benign adenomas, and no lymphomatous infiltrate was noticed. Alemtuzumab was started, eliciting partial improvement with healing of ulcerations, although infiltrated patches persisted. At that time, the patient had to interrupt follow-up. When he resumed medical consultation 6 months later, ulcerations had recurred, complicated by debilitating pain. Laboratory findings remained unmodified and the same TCR-gamma chain clone was evidenced in biopsies. Hypermetabolic uptake remained focused on acral areas on PET. A bexarotene regimen was started, but was not tolerated, so was replaced by pegylated liposomal doxorubicin (at 40 mg/m<sup>2</sup> per 3 weeks) inducing partial healing of lesions after 3 injections. The treatment was complicated with palmo-plantar erythrodysesthesia syndrome and switched to non-pegylated liposomal doxorubicin. Ulcerations healed in 6 months, while slight residual infiltrated patches on the nose and toes persisted. While the treatment had been maintained for 8 months, the patient died at home of unrelated condition, 4 years after the symptoms had arisen.

Although AVS can complicate the course of systemic lymphomas (2), it has not been linked to cutaneous lymphoma.

## DISCUSSION

We initially wondered whether this condition represented an unusual vasculitis. However, virtually all cases of vasculitis-induced acral necrosis display at least one of the following: angiographic abnormalities, leukocytoclastic vasculitis, giant cell arteritis, systemic symptoms, or circulating cryoglobulinaemia (3). AVS-related lymphoid infiltrates have not been thoroughly histologically studied, but cutaneous lymphocytic vasculitis does not display overt atypia, as seen here (4). We also wondered whether this disorder might be subsequent to immune dysregulation triggered by hepatitis B virus. This seems unlikely, as no viral replication or abnormalities of B-cell lymphocytes were evidenced. Likewise, no improvement was noted after the introduction of antiviral treatment.

We ruled out that this case might be a variant of subcutaneous panniculitis-like T-cell lymphoma (SPTL), which is a cytotoxic CD8<sup>+</sup> T-cell lymphoma of alpha/beta lineage. This typically presents with non-ulcerating nodules or plaques in the legs associated with systemic symptoms (5). Subcutaneous panniculitis-like T-cell lymphoma infiltrate primarily the subcutis, sometimes extending to overlying dermis. They consist in CD8<sup>+</sup> cytotoxic T cells of alpha/beta lineage, as in our case. However, our patient's lesions were restricted to acral skin, and lymphomatous infiltrates were confined to the dermis without associated lobular panniculitis or adipocyte rimming.

The presence of angiodestruction also raised a suspicion of cutaneous gamma/delta T-cell lymphoma (CGD-TCL) and extranodal NK/T-cell lymphomas (EN-NKTCL), but their clinical and immunophenotypic presentations differ from our case. Both present with ulcerated nodules or tumours in the extremities or trunk. CGD-TCL consists of gamma/delta T cells expressing CD56 and TCR-delta, while CD8 and beta F1 are negative (6). EN-NKTCL infiltrate the dermis, along with prominent angiocentricity and express CD56 and EBER (7).

Immunophenotype of our case is reminiscent of primary cutaneous aggressive epidermotropic CD8<sup>+</sup> cytotoxic T-cell lymphoma. However, this entity presents with disseminated necrotic papulo-nodules, and epidermotropism is a diagnostic hallmark (8). Altogether, the clinicopathological features of this case do not fit any of the entities endorsed by 2005 World Health Organization – European Organization for Research and Treatment of Cancer (WHO-EORTC) (7) or 2008 International Agency for Research on Cancer classifications (9).

We report here a case of CD8<sup>+</sup> CTCL mimicking AVS. We ask whether this case represents an underdiagnosed form of CTCL, as infiltrated lesions may be overlooked at the edge of acral ulcerations. These findings emphasize the need to characterize further AVS-associated lymphoid infiltrates. Cutaneous lymphoma should be a diagnostic consideration in autoantibody-negative AVS, especially when accompanied by infiltrated patches, or when no improvement occurs under treatment.

*The authors declare no conflicts of interest.*

## REFERENCES

1. Poszepczynska-Guigne E, Viguier M, Chosidow O, Orcel B, Emmerich J, Dubertret L. Paraneoplastic acral vascular syndrome: epidemiologic features, clinical manifestations, and disease sequelae. *J Am Acad Dermatol* 2002; 47: 47–52.
2. Garioch JJ, Todd P, Soukop M, Thomson J. T-cell lymphoma presenting with severe digital ischaemia. *Clin Exp Dermatol* 1991; 16: 202–203.
3. Pipitone N, Holl-Ulrich K, Gross WL, Lamprecht P. Unclassified vasculitis with acral ischemic lesions: “forme fruste” or idiopathic vasculitis? *Clin Exp Rheumatol* 2008; S41–S46.
4. Carlson JA, Chen KR. Cutaneous vasculitis update: neu-

- trophilic muscular vessel and eosinophilic, granulomatous, and lymphocytic vasculitis syndromes. *Am J Dermatopathol* 2007; 29: 32–43.
5. Willemze R, Jansen PM, Cerroni L, Berti E, Santucci M, Assaf C, et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. *Blood* 2008; 111: 838–845.
  6. Toro JR, Liewehr DJ, Pabby N, Sorbara L, Raffeld M, Steinberg SM, et al. Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma. *Blood* 2003; 101: 3407–3412.
  7. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005; 105: 3768–3785.
  8. Berti E, Tomasini D, Vermeer MH, Meijer CJ, Alessi E, Willemze R. Primary cutaneous CD8-positive epidermotropic cytotoxic T cell lymphomas. A distinct clinicopathological entity with an aggressive clinical behavior. *Am J Pathol* 1999; 155: 483–492.
  9. Swerdlow SH. WHO classification of tumours of hematopoietic and lymphoid tissues. Lyon: IARC Press; 2008.