Update on primary cutaneous T-cell lymphomas rare subtypes

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Abstract

Rare subtypes of cutaneous T-cell lymphomas (CTCL) include four entities, primary cutaneous γδ T-cell lymphoma, primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma, and primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorders, primary cutaneous acral CD8+ T-cell lymphoma, which were previously considered provisional and are now included in the new 5th World Health Organization classification of hematolymphoid tumors as distinct entities. An updated summary of the clinical, histological, and genomic characteristics of these uncommon CTCL subtypes is given in this review, with a focus on the growing body of knowledge regarding their classification and possible treatment strategies.

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Key words: cutaneous lymphoma; rare cutaneous lymphoma; aggressive lymphoma; T follicular helper phenotype.

Contributions: SAV, conceptualization, design, writing, editing, and literature review; EB, edited and supervised the manuscript. All the authors approved the final version to be published.

Conflict of interest: the authors declare no conflict of interest.

Funding: none.

Consent for publication: the patients gave their consent for the publication of this article and any accompanying images.

Received: 1 February 2024.
Accepted: 15 February 2024.

Dermatology Reports 2024; 16;(s2):9961
doi:10.4081/dr.2024.9961

Introduction

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of cutaneous lymphoproliferative disorders (LPD) characterized by neoplastic proliferation of clonal T-cells in the skin. CTCL represents approximately 75-80% of all primary cutaneous lymphomas; mycosis fungoides (MF) and CD30+ LPD are the most frequent entities.[1] Since the 2008 WHO classification of tumors of hematopoietic and lymphoid tissues,[2] three entities have been included in the rare subtype group, primary cutaneous γδ T-cell lymphoma (PCGD-TCL), primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (PCAECx-TCL), and primary cutaneous CD4+ small/medium T-cell lymphoma, recently renamed as primary cutaneous CD4+ small/medium T-cell LPD (PCSM-LPD).[3,4] These two last entities and the fourth subtype, added in 2017,[3] primary cutaneous acral CD8+ T-cell lymphoma (ACD8-LPD), were considered provisional entities until the recent 5th WHO Haematolymphoid Tumours edition,[5] where they are listed as separate entities. Defining "rare" as a frequency of less than 1%, three additional CTCLs should be incorporated: subcutaneous panniculitis-like T-cell lymphoma, extranodal NK-T lymphoma, nasal type, and cutaneous peripheral T-cell lymphoma, not otherwise specified, but these have been recognized as distinct entities since the 2005 and 2008 EORTC/WHO classifications and not included in CTCL, rare subtypes.[2]

Primary cutaneous γδ T-cell lymphoma

PCGD-TCL is a cytotoxic cutaneous lymphoma characterized by a clonal proliferation of mature activated γδ T-cells in the skin and an aggressive clinical course.[4] PCGDTCL occurs mainly in adults without sex predilection. This entity was first described simultaneously in 1991 by Berti *et al.*[6] for its epidermotropic variant and by Burg *et al.*[7] for its subcutaneous variant, which was compared and differentiated from the αβ primary cutaneous subcutaneous panniculitis-like lymphoma characterized by a different clinical course. Due to the scarcity of immunohistochemical γδ markers, for many years LPD with a γδ phenotype were included in this rare subtype, but recently, thanks to the increased use of immunohistochemical markers on paraffin-embedded tissues, the presence of the γδ phenotype has also been found in different cutaneous LPD, such as MF and lymphomatoid papulosis. These findings have demonstrated that the presence of γδ cells does not necessarily correlate with an aggressive course, fixing the clinicopathological definition of PCGD-TCL.[8,9]

PCGD-TCL is characterized by two clinical presentations, which correlate with different histological features (Figure 1).[4] The clinical picture may be characterized by erythematous and scaling patches and plaques or by deep dermal or subcutaneous tumors, often covered by skin patches. Histologically, three patterns are recognized: epidermal, dermal, and subcutaneous, which may occur together in the same patient. Dermal-epidermal forms (DE-GDTCL) are characterized by an infiltrate in the dermis with

focal epidermotropism to marked pagetoid infiltrate. The main differential diagnosis is MF.[10] In the subcutaneous forms (S-GDTCL), the neoplastic cells tend to rim the fat cells as in the subcutaneous panniculitis-like lymphoma, but often the presence of a dermo-epidermal infiltrate is associated. In all cases, neoplastic cells are characteristically positive for T-cell receptor (TCR) gamma/delta, CD3, CD2, and CD56 and negative for beta-F1, CD5, CD4, and CD8.[11] The different clinic-histological presentation of PCGD-TCL has been genomically correlated with two cells of origin located in different compartments: DE-GDTCL derives from TCRVδ1 cells, which are predominantly present in the outer cutaneous layers, while S-GDTCL derives from TCRVδ2 cells, which are predominantly present in the fat.[12] Cases of classic MF characterized by the appearance of nodules, histologically typical for PCGD-TCL, have also been described in independent series,[9,13] probably due to clonal selection of γδ T-cells minimally present in the initial MF lesions. These forms were found to be TCRVδ1+. The genomic landscape of PCGD-TCL is also characterized by frequent mutation of STAT3, STAT5B and multiple oncogenic pathways, including MAPK signaling (KRAS, NRAS, MAPK1), MYC pathway (MYC, MYCN, FBXW7), JAK/STAT signaling (STAT3, STAT5B, JAK3, SOCS1), and chromatin modification (ARID1A, TRRAP, TET2, KMT2D).[12,14]

The prognosis of PCGD-TCL is poor with a median survival of 12 months, especially in S-GDTCL, instead, DEGD-TCL shows firstly an indolent course followed by a rapid evolution.[15] Other poor prognostic factors include age >40 years, CD56 and CD95 expression, CD8 negativity, central nervous system involvement, and hemophagocytic syndrome.[16] Currently, the treatment of PCGD-TCL is still based on aggressive chemotherapy due to its prognosis. The most common chemotherapy schemes reported are similar to those of peripheral T cell lymphomas, such as anthracycline-based with either cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone (CHOP) or etoposide+CHOP (EPOCH).[17] Recently, literature has reported cases successfully treated with brentuximab vedotin and mogamulizumab.[17-19] On the basis of genomic findings, new clinical trials can be further considered, such as Jak-inhibitors. Allogeneic stem cell transplantation should also be considered.

Primary cutaneous CD8+aggressive epidermotropic cytotoxic T-cell lymphoma

PCAECx-TCL is a rare and aggressive cutaneous lymphoma characterized by an epidermotropic proliferation of CD8+ cyto-

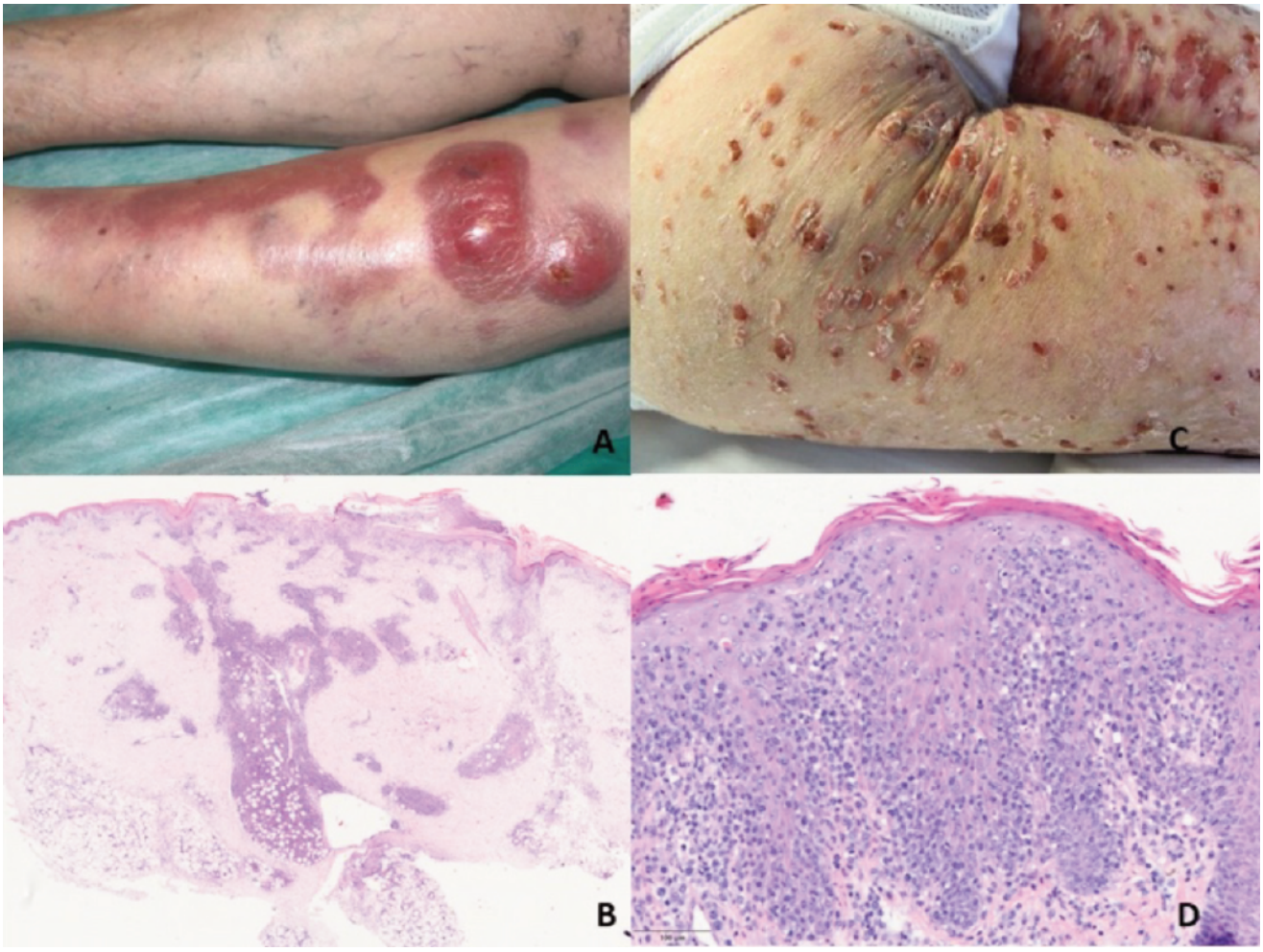

Figure 1. Primary cutaneous γδ T-cell lymphoma. **A**) Erythematous plaques and nodules on legs; **B**) dermal and subcutaneous involvement of the infiltrate. H&E, 40×; **C**) crusted and scaling plaques on the legs; **D**) marked epidermotropic infiltrate of medium-sized hyperchromatic lymphocytes and some blasts. H&E, 200×.

toxic T-cell, first reported by Berti *et al.* in 1999.[4,20] PCAECx-TCL typically occurs in adults, even if pediatric anecdotical cases have been reported.[21] Clinically, PCAECx-TCL can be characterized by diffuse crusted or ulcerated patches/plaques or papulo-nodules and/or localized, mainly acral, tumors (Figure 2). Clinical presentations vary from erythema multiforme-like to large ulcerations like pyoderma gangrenosum.[22,23] Mucosal involvement is frequent. Necrosis and blisters are described as autoimmune bullous diseases.[24] A prodromic phase with indolent psoriasiform dermatitis or MF-like lesions is possible, demonstrating the diagnostic challenge.[25,26] The disease course is aggressive with a median survival of 12 months and dissemination to unusual sites, such as the lung, testis, and central nervous system, sparing lymph nodes. Histologically, a band-like or diffuse infiltrate of small-medium or medium-large T-cells with focal or marked pagetoid epidermotropism is typically evident.[20] In some cases, epidermotropism could be minimal and infiltrate deeper into the dermis. Follicolotropism is frequent.[1] Compared to the typical immunophenotype originally described, characterized by the expression of βF1, CD45RA, CD3, CD7, CD8, Tia1, granzyme B and perforin and the absence of CD2, CD54, CD5, and CD45RO, some cases can be CD8 negative or dim, leaving more difficulties in differential diagnosis.[20,26] EBV is negative but CD56 could occasionally be positive.[26] Genomic studies revealed a great instability with numerous genomic aberrations, losses more than gains, such as the more significant in the region containing CDKN2A/B.[27] Recent studies suggested a co-activation of JAK2 signaling (via STAT3) and NF-κB signaling, demonstrating that overactivation of JAK2 signaling could play a pivotal role in the pathogenesis of PCAECxTCL.[28] These findings opened a new therapeutic possibility with JAK2 inhibitors, like ruxolitinib, alone or in combination with NF-κB inhibitors (*e.g.*, bortezomib, dimethyl fumarate) for this aggressive disease, which is characterized by resistance to conventional chemotherapy and no evidence-based therapeutic options.[28] When possible, alloSCT should be considered.

Primary cutaneous CD4+small/medium-cell lymphoproliferative disorder

PCSM-LPD is a distinct entity, which since its first description in 1995,[29] has been the object of debate about its exact nosology.[5] PCSM-LPD was renamed from lymphoma to lymphoprolif-

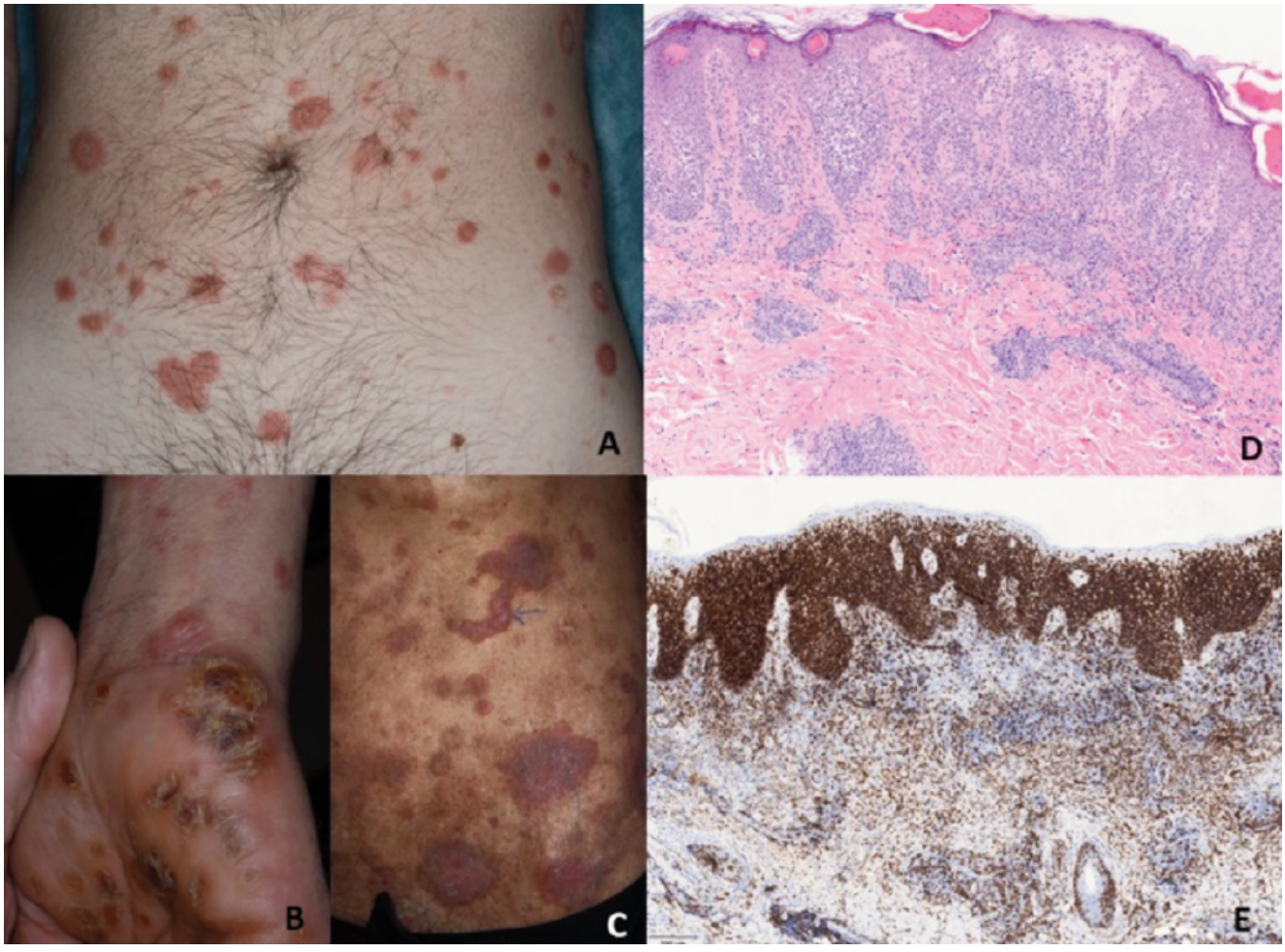

Figure 2. Primary cutaneous CD8+aggressive epidermotropic cytotoxic T-cell lymphoma. **A**) Diffuse scaling and crusted plaques on the abdomen; **B**) erythematous plaques with crusts on the arm and palm; **C**) diffuse brownish and violaceous plaques; **D**) an infiltrate in the upper dermis of small/medium lymphocytes and marked epidermotropism. (H&E, 100×); **E**) CD8 staining reveals the marked epidermotropism of the neoplastic cells (H&E, 100×).

erative disorder because of its indolent clinical behavior and uncertain malignant potential.[3,4] Based on the last WHO classifications, PCSM-LPD includes only a single nodule, mainly located in the head and neck area.[4,5] Multiple lesions can be present but MF-like plaques appearance is now not listed and should be considered a variant of MF.[30] Histologically, a dense or nodular or diffuse infiltrate of small/medium-sized T pleomorphic cells is evident in the whole dermis to the upper part of the subcutaneous fat (Figure 3). Epidermotropism is usually absent. T-cells are typically CD4+ and PD1+ and arranged around large blasts or B-cells, forming rosettes. Numerous reactive cells, such as eosinophils and plasma cells, are mixed with neoplastic clonal T cells. Considering these characteristics, differential diagnosis with pseudolymphomas could be a challenge, even if PCSM-LPD shows in most cases a clonal rearrangement of the TCR.[4] PCSM-LPD is characterized by CD4+ T follicular helper (TFH) phenotype (PD1/CD279+, Bcl6+, ICOS/CD278+, CXCL13+, CD10+, CXCR5-), even if the complete expression of all TFH markers together is not always present.[31] Nowadays, TFH phenotype in cutaneous LPD is the purpose of numerous studies. Its expression is evident not only in PCSM-TDL, but also in other cutaneous lymphomas, such as MF, even if clinicopathological presentation in these cases appears to have peculiar characteristics distinguishing it from classic MF, and its definition is still in progress.[32,33] The excellent prognosis of PCSM-LPD has been confirmed by genomic studies which have not seen any known pathogenic T-cell lymphoma-associated mutations.[34] Management of disease includes surgical excision, radiation therapy, and topical or intralesional steroids.

Primary cutaneous acral CD8+ lymphoproliferative disorder

ACD8-LPD is a rare disease, renamed as lymphoproliferative disorder in the last 5th WHO classification because of its indolent course.[5] ACD8-LPD is now listed as a separate entity because of its specific and reproducible clinicopathological characteristics, which allow the differentiation with other dermal CD8+ proliferations, such as primary cutaneous CD8+ peripheral T-cell lymphoma, unspecified and cutaneous CD8+ lymphoproliferations associated with congenital immunodeficiency syndromes, and avoid aggressive treatment. ACD8-LPD was first described by Petrella *et al*.[35] in 2007 as indolent CD8-positive lymphoid prolif-

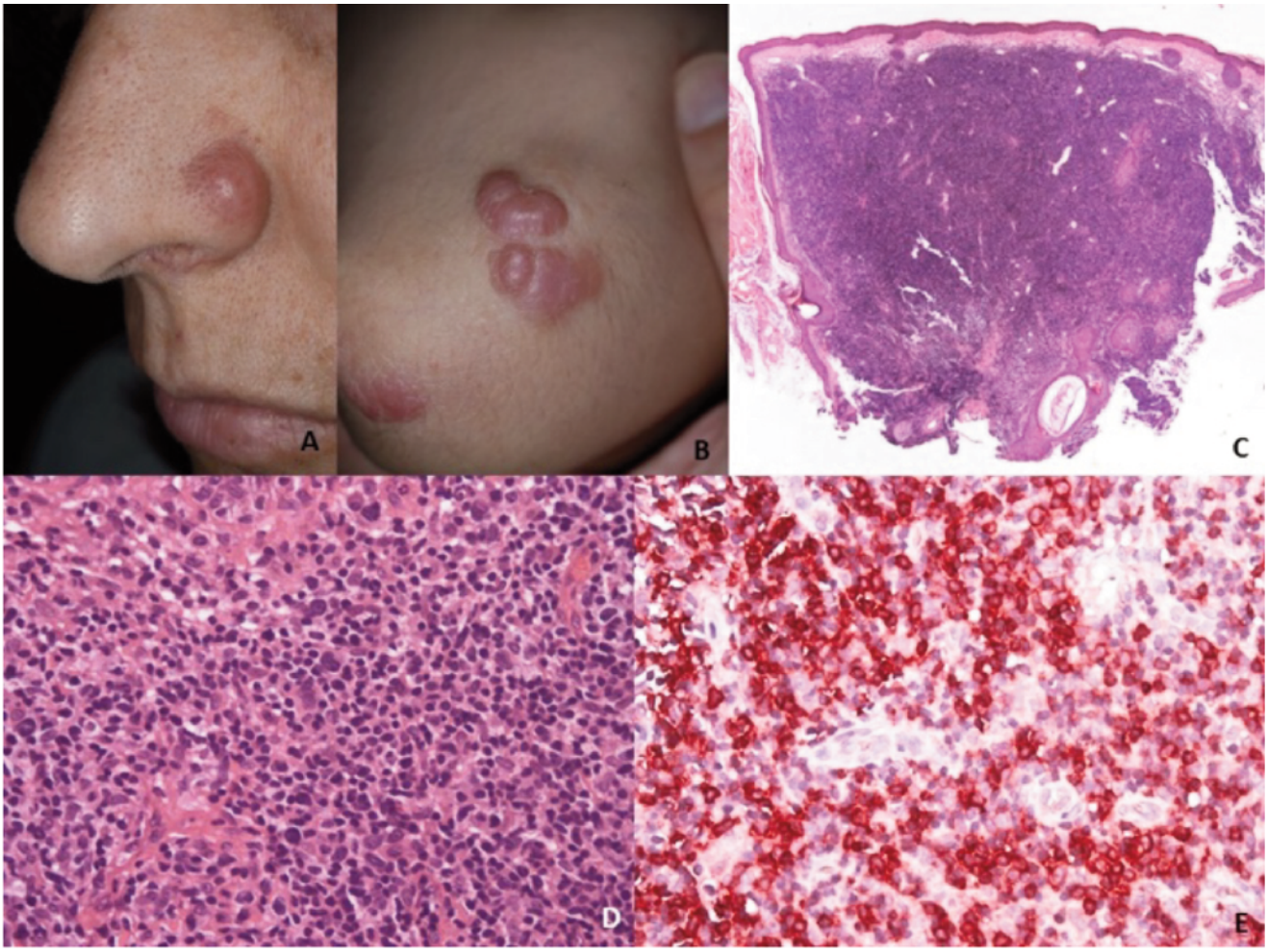

Figure 3. Primary cutaneous CD4+small/medium-cell lymphoproliferative disorder. **A**) A typical nodule on the nose; **B**) multiple nodules on the elbow; **C**) a dense diffuse infiltrate in the whole dermis, sparing the epidermis (H&E, 40×); **D**) at higher magnification, the infiltrate is composed of small/medium-sized hyperchromatic lymphocytes mixed to large cells (H&E, 200×); **E**) PD1 staining reveals that small lymphocytes are arranged in rosettes (immunophosphatase, 200×).

eration of the ear and now includes by definition single papules or nodules localized on acral sites, especially ear, and nose, even if other acral sites, such as feet, or non-acral sites, such as thighs, eyelids, and trunk, have been reported.[36] Histologically, the infiltrate is typically non-epidermotropic, dense, micronodular, and diffuse, constituted by small/medium-sized lymphocytes with a monocytoid appearance, including an eccentric nucleus and a reniform nuclear outline.[1] Phenotypically, the cells express CD8 and TIA but are typically granzyme negative, as in cytotoxic CD8+ T-cells without an activated phenotype.[37] CD68 is uniquely positive in this form of cutaneous CD8+ lymphoproliferative disorder; the staining pattern exhibits a distinctive perinuclear localization.[36] The proliferation index is low. A monoclonal rearrangement of the TCR is usually present.

The prognosis is favorable with only skin relapses, except for one case reported in the literature with extracutaneous involvement.[37,38] Considering the indolent course, treatment modalities include surgical excision and local radiotherapy. Spontaneous regression is possible.

Conclusions

Rare subtypes of CTCL included four different disorders, primary cutaneous γδ T-cell lymphoma, primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma, primary cutaneous CD4+ small/medium T-cell lymphoma, and primary cutaneous acral CD8+ lymphoproliferative disorder. During the last few years, the definition of genetic and clinicopathological characteristics has permitted to list these entities as separate, differentiating the cases that do not fulfill these criteria and object of further investigations in the future.

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