with a specific myeloma immunoglobulin type, although a more aggressive course is observed in light-chain-only subtypes [10]. Requena et al. [11] analyzed 8 cases of cutaneous plasmacytoma and revealed that malignant plasma cells are homogeneous in their immunophenotype with strong expression of CD79a, CD138, and epithelial membrane antigen. In addition, RBL gene deletion in skin-infiltrated plasmacytes was reported to be associated with poor prognosis [11]. A recent retrospective study of 53 cutaneous plasmacytoma cases showed no correlation between CD56 negativity or cytogenetic abnormality with skin infiltration of malignant plasma cells and that the plasmablastic morphology in the skin lesion indicated a worse overall survival [10]. In the present case, the malignant plasma cells were positive for CD138 and negative for CD56, CD19, CD20, and CD22, which correlated to the immunophenotypic characterization of malignant plasma cells. The RBL1 gene deletion could not be analyzed, and no significant plasmablastic appearance of plasma cell infiltration was observed in the patient’s skin lesion.

Although hemophagocytosis by neoplastic plasma cells does not appear to be associated with a specific immunophenotype, immunoglobulin or light-chain subtype, or karyotype [6]. One hypothesis is that hemophagocytic plasma cell formation may be attributed to the expansion of rare B-cell clones with innate phagocytic potential, although this proposition remains to be confirmed [5, 7]. Similar to our case, the hemophagocytic feature of plasma cells is more frequently found in female patients, and it appears to be dominant in mature erythrocytes and platelets [4, 7]. Some reports also suggest that hemophagocytosis by neoplastic plasma cells resulted in peripheral blood cytopenia; however, whether this complication is a direct consequence of hemophagocytosis by plasma cells remains to be determined [2, 4].

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Differential diagnosis of primary cutaneous CD4+ small/medium T-cell lymphoproliferative lesions: A report of three cases

TO THE EDITOR: Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (CD4+ PCSTM-TLPLD) is characterized by the proliferation of small-to-medium-sized T-helper lymphocytes within the dermis. According to the 2016 World Health Organization (WHO) classification, the diagnosis of CSMTLPLD is considered excellent, and it should not be diagnosed as lymphoma [1]. We studied three cases of CD4+ PCSTM-TLPLD, focusing on its clinicopathological characteristics and differential diagnoses.
Cases

Most patients were middle-aged men who presented with solitary, reddish nodules in the head (Fig. 1). In all three cases, radiological evaluation revealed intradermal cellular nodules, without involvement of the surrounding soft tissue or bone. The nodules of three cases measured 2.7 cm, 1.5 cm, and 0.6 cm in the greatest dimension. In two cases, complete excisions were performed without adjuvant treatment. Both patients were followed-up for 5 and 9 months, respectively, and no adverse events were reported during this period. Case 3 showed complete remission after excision and local radiotherapy, with no evidence of disease for 89 months (Table 1).

All three cases were characterized by a typical dense, nodular, or diffuse lymphoid infiltrate, involving the entire dermis (Fig. 2A). Intraepithelial lymphocytosis was sparse; therefore, no definite epidermotropism was observed. There was a grenz zone just under the epidermis (Fig. 2B). The infiltrate was composed of small-to-medium-sized lymphocytes with mild pleomorphism and was occasionally admixed with B cells and plasma cells (Fig. 2C). The immunohistochemical profile of the tumor cells was as follows: CD20-, CD3+, CD4+, CD8-, PD1+, CXCL13+, and Bcl2+, supportive of follicular helper T-cell (TFH) phenotype. The Ki-67 labeling index was less than 10% (Fig. 2D-J).

Discussion

The CD4+ PCSM-TLPD was first described in 1995 by Friedmann et al. [2] as a ‘primary cutaneous CD4+ small/medium T-cell lymphoma’, and this entity was classified as a provisional lymphoma in the previous WHO classification [3]. Patients with CD4+ PCSM-TLPD usually present with solitary, reddish tumors, commonly located on the head and neck, with rare instances of ulceration. Spontaneous resolution was observed after an incisional biopsy, and the overall 5-year survival rate was reported to be 60–100%. In particular, the localized lesions showed excellent prognosis, prompting some to consider CD4+ PCSM-TLPD to be a form of reactive lymphoid lesion. With the present knowledge, it remains unclear if CD4+ PCSM-TLPD is a precursor of lymphoma, representing a subtype of cutaneous T-cell lymphoma, or if it is an entirely benign reactive condition (pseudolymphoma) [4].

Garcia-Herrera et al. [5] reported five patients who died of CD4+ PCSM-TLPD. The patients with poor prognosis had characteristic features, such as a larger lesion (>5 cm), higher proliferation indices, decreased expression of CD4, and more monotonous infiltrates, with significantly decreased numbers of background inflammatory cells. The cases we studied did not demonstrate any of the above features.

The differential diagnoses of CD4+ PCSM-TLPD comprise a spectrum of characterizations, including distinct lymphomas, such as the primary cutaneous acral CD8+ T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified (PTCL, NOS), and nodular phase of mycosis fungoides (MF), to benign reactive lymphoid hyperplastic conditions, such as T-cell pseudolymphoma.

Primary cutaneous acral CD8+ T-cell lymphoma may be clinically indistinguishable from CD4+ PCSM-TLPD. However, it presents with a more monotonous infiltrate with a CD8 (cytotoxic) phenotype. Clinically, this type of T-cell lymphoma commonly develops in the ears. In both diseases, the lesions are dermal nodules with no distinct epidermotropism, and show an indolent course [6]. The long-term follow-up of both diseases shows excellent outcomes; complete remission was observed in 100% of the cases (22 CD4+ PCSM-TLPD and 3 CD8+ T-cell lymphoma

| Table 1. Clinical summary of three primary cutaneous CD4+ small/medium T-lymphoproliferative disorder cases. |
|---|---|---|---|---|---|---|
| Age | Gender | Site | No. | Size (cm) | Shape | Tx | F/U (mo) | Result |
|---|---|---|---|---|---|---|---|---|
| 1 | 48 | M | Scalp | Single | 2.7 | Nodular | Ex | 9 | NE |
| 2 | 42 | M | Forehead | Single | 1.5 | Nodular | Ex | 5 | NE |
| 3 | 56 | F | Cheek | Single | 0.6 | Nodular | Ex+RTx | 89 | CR |

Abbreviations: CR, complete remission; Ex, excision; F/U, follow up; mo, month; NE, no event; RTx, radiotherapy; Tx, treatment.
Fig. 2. (A) Scanning microscopy showed a nodular mass, occupying the entire dermis and subcutis along the fascia (Hematoxylin-Eosin stain, ×10). (B) The epidermis showed no definite epidermotropism with a subepidermal grenz zone (Hematoxylin-Eosin stain, ×40). (C) The cells are bland-looking, small-to-medium-sized lymphocytes (Hematoxylin-Eosin stain, ×400). The tumor cells are positive for CD3 (D) and CD4 (E) and negative for CD20 (F) and CD8 (G), indicating a helper T-cell phenotype. Tumor cells are also positive for PD1 (H) and CXCL13 (I), suggestive of a follicular helper T-cell phenotype. The Ki-67 proliferative index was low at 10% (J).

Primary cutaneous follicular helper T-cell lymphoma and cutaneous angioimmunoblastic T-cell lymphoma (AITL) share the same immunophenotype (PD1, ICOS, CXCL13, CD10, and Bcl6). Similar to nodal AITL, both diseases show Epstein–Barr virus positivity. Overall, patients with AITL have an aggressive form of the systemic disease [8].

The tumor phase of MF may histopathologically be confused with that of CD4+ PCSM-TLPD. MF lesions are characterized by dense, dermal infiltrates of small-to-medium-sized CD4+ T cells. Despite the histopathological similarity, the clinical features help distinguish these two entities. Patients with MF have a long history of patches and plaques, typical of MF [9]. The histomorphology of the patients studied herein showed nodular proliferation without distinct epidermotropism.

In conclusion, the prognosis of CD4+ PCSM-TLPD is favorable, and it should be differentiated from other aggressive forms of the disease, such as cutaneous T-cell lymphoproliferative disorder and pseudolymphoma. A clinicopathological correlation is very important to avoid diagnostic pitfalls, especially in a small punch biopsy.

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A young man with acute respiratory distress syndrome: eosinophilia is not always “benign”

TO THE EDITOR: Internists in intensive care units often encounter cases of acute respiratory distress syndrome (ARDS) that require mechanical ventilation. Such cases are difficult to manage and have a grim prognosis. Potential causes of ARDS include sepsis, trauma, pneumonia, infection, and uremia [1]. We describe a case of ARDS with associated eosinophilia that was diagnosed as a myeloid neoplasm with associated eosinophilia and PDGFRA gene rearrangement. Timely administration of imatinib mesylate saved the patient’s life without the need for invasive ventilation.

A 35-year-old man presented to our emergency department after coughing for 7 days and experiencing respiratory distress for 1 day. He had no history of fever, nasal discharge, chest pain, hemoptysis, hematuria, or passage of worms in his stool. He denied any atopy, recent travel, or exposure to pets, birds, cotton, dust, or metal fumes. His vital signs were as follows: blood pressure, 110/70 mmHg; pulse rate, 112 beats/minute; and respiratory rate, 30 breaths/minute. Remarkably, a general examination showed the presence of pallor and the use of the accessory muscles of respiration. There was no lymphadenopathy, cyanosis, clubbing, pedal edema, or palpable purpura, and the jugular venous pressure was not elevated. Bilateral rhonchi and crackles were audible on chest auscultation. The liver (4 cm in size) and spleen (5 cm in size) were palpable on abdomen examination. The results of a cardiovascular and neurological examination were unremarkable. A complete blood count revealed an hemoglobin level of 8.3 g/dL; white cell count of 27.6 x 10^9/L; a differential count of 39% polymorphs, 11% lymphocytes, 2% monocytes, and 48% eosinophils (absolute eosinophil count, 13.2 x 10^9/L); a platelet count of 420 x 10^9/L; and an erythrocyte sedimentation rate of 24 mm/hour. Serum levels of lactate dehydrogenase (LDH) and uric acid were 1,000 U/L and 565 μmol/L, respectively, and renal and liver function were normal. The results of an arterial blood gas analysis were consistent with type-1 respiratory failure: pH, 7.38; partial pressure of oxygen, 67 mmHg; partial pressure of carbon dioxide, 35.5 mmHg; and oxygen saturation, 85%.

A chest X-ray revealed bilateral fluffy alveolar opacities (Fig. 1A). Cardiac size and contour were normal. Contrast-enhanced computed tomography of the chest revealed symmetrical confluent airspace opacities in the bilateral central lung fields, suggestive of pulmonary edema. The patient’s symptoms did not improve and type-1 respiratory failure worsened; hence, bronchoscopy was performed. Bronchoalveolar lavage revealed an eosinophil-rich infiltrate, and histopathological examination of a transbronchial lung biopsy showed fibroelastic proliferation with formation of Masson bodies in the alveolar spaces (suggestive of organizing pneumonia).

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