Primary cutaneous CD4⁺ small- to medium-sized pleomorphic T-cell lymphoma (SMPTCL) is listed as a provisional entity in the recent World Health Organization–European Organization for Research and Treatment of Cancer classification. Interestingly, SMPTCL is characterized by an indolent clinical course and a worrying histopathological appearance.

Report of a Case

We report the case of a 21-year-old woman diagnosed as having the very rare entity primary cutaneous CD4⁺ SMPTCL. The patient was referred to our clinic with a 5-year history of a slowly growing tumor on the right cheek. Despite occasional pruritus the patient did not report any further complaints. Topical treatment with antibiotics (fusidic acid and erythromycin) and antifungal drugs did not result in improvement. On physical examination the patient presented a solitary, sharply demarcated erythematous tumor on the right cheek (Figure 1A). The physical examination did not reveal either lymphadenopathy or hepatosplenomegaly.

Histopathologic findings showed a dense, nodular, lymphoid infiltrate in the entire dermis. The infiltrate was composed of small- to medium-sized pleomorphic lymphocytes with few large cells. The lymphocytes showed cytologic atypia with irregular nuclear membranes, hyperchromatic nuclei, and numerous mitotic figures. Focally there was striking epidermotropism of lymphocytes with exocytosis into the epidermis and pilosebaceous units and folliculotropism (Figure 2). Immunohistochemical analysis showed that the infiltrating T cells were positive for CD4 and coexpressed CD5 (Figure 2C and D). Most of the CD4⁺ T cells were negative for CD8 and positive for CD10 (Figure 2E) and showed nuclear expression of Bcl-6 (data not shown), CD30⁺ CD4⁺ T cells were not observed (data not shown). The overall proliferation rate (of Ki-67) was low; nevertheless, focally up to 30% of CD3⁺ T cells were positive for Ki-67. In addition, numerous disseminated CD20⁺ B lymphocytes with focal germinal center formation were observed in the infiltrate (Figure 2). Although the...
infiltrate was predominantly composed of lymphocytes, it was intermingled with numerous histiocytes. Clonality analysis of the T-cell–receptor gamma gene showed a polyclonal smear. Complete blood cell count, serum protein electrophoresis, fluorescence-activated cell sorting analysis, basic metabolic panel, and parameters for kidney and liver function were without pathologic findings. β2-Microglobin and soluble CD25 levels were within standard values. Tests for Sézary cells, as well as anti-Borrelia burgdorferi antibodies, were negative. Chest radiography and abdominal and lymph node ultrasonography did not reveal any abnormalities.

Because of the numerous CD20+ B cells, which represented almost half of the infiltrate, the absence of signs of systemic disease and the expected positive side effect profile, we initiated a therapy with oral doxycycline monohydrate, 200 mg daily for 21 days. After 6 weeks the clinical reexamination showed complete remission of the tumor on the right cheek (Figure 1B).

Thirteen months later the patient was again referred to our clinic with erythematous, unsharply demarcated, and scaly plaques of the right cheek (Figure 1C). We decided to take a second skin biopsy specimen.

Histopathologic findings revealed a very similar pattern compared with the skin biopsy taken 1 year before. Immunohistochemical analysis showed that most of the infiltrating CD4+ T cells coexpressed CD3 and CD5. Furthermore, CD4+ T cells were positive for CD10 and had nuclear expression of Bcl-6.
but were negative for CD56, granzyme B, perforin, TIA1, and TdT. Compared with the biopsy specimen taken 13 months before, histopathologic findings showed fewer CD20+ B lymphocytes in the infiltrate. They were scattered throughout the infiltrate and did not form nodular aggregates or lymph follicles. In summary, histopathologic findings confirmed the diagnosis of a relapse of the SMPTCL. Clonality analysis again revealed polyclonal amplification of the T-cell–receptor gamma gene.

Renewed blood analysis and staging procedures again did not show any abnormalities. We then initiated topical treatment with mometasone furoate, 0.1% twice daily for 2 weeks followed by once daily for 2 weeks. After 4 weeks of treatment the patient achieved complete remission. To date (6 months after the second biopsy), the patient still has no signs of systemic disease. Nevertheless, we initiated long-term follow-up care of this patient at our dermato-oncology outpatient department.

Discussion

Primary cutaneous lymphomas represent a heterogeneous group of neoplasms that show considerable variation in histologic appearance, immunophenotype, clinical presentation, and prognosis. In the recent World Health Organization (WHO)–European Organisation for Research and Treatment of Cancer classification on cutaneous lymphomas1 and in the new WHO classification of tumors of hematopoietic and lymphoid tissues,2 primary cutaneous CD4+ SMPTCL is included as a provisional entity that represents only about 3% of all primary cutaneous lymphomas. SMPTCL usually has a relatively favorable prognosis with an estimated 5-year survival rate of 60% to 80%.3 To date, only a few and heterogeneous series of cases of SMPTCL have been reported.3 Most reported cases share the incongruity between the indolent clinical behavior and the worrying histopathologic and molecular features. One of the greatest case series of SMPTCL was published by Beltaminelli et al.3 They evaluated 136 patients (median age, 53 years [range, 3-90 years]) with mostly solitary lesions on the head and neck area (75%). Monoclonal rearrangement of the T-cell–receptor gamma gene was found in 60% of tested cases. As in most of the cases reported by Beltaminelli et al,3 the atypical T lymphocytes in our case predominantly showed a CD3+ /CD4+ /CD8− /CD30 immunophenotype. Furthermore, the numerous B cells detected in the skin biopsy specimen of our patient are in accordance with the findings of Beltaminelli et al3; in all tested cases they observed variable numbers of B lymphocytes, sometimes representing almost half of the infiltrate. The prominent B-cell infiltrate may cause problems in the distinction from cutaneous B-cell lymphomas, particularly extranodal marginal zone B-cell lymphoma, which has a similar polymorphous background.3 The often present follicular helper T cells (CD4+, CD10+, Bcl-6+) might stimulate B cells, thus explaining the numerous B cells frequently found in SMPTCL.4 It has been shown that, on stimulation, the follicular helper T cells promote germinal center B-cell survival and differentiation and allow immunoglobulin class switching and somatic hypermutation.5,6

In view of the histologic pattern with remarkable numerous B cells and encouraged by the well-accepted effectiveness of doxycycline in B-cell pseudolymphoma, we decided to initiate a therapy with oral doxycycline, which led to a complete remission of SMPTCL in our patient.

Doxycycline is a relatively nontoxic drug that has been approved for human use for a long time, and it has become increasingly apparent that doxycycline may have pleiotropic effects, including nonantibiotic activities.7 Some publications have reported doxycycline-induced tumor regression via inhibition of tumor cell proliferation and/or apoptosis8,9 and inhibition of angiogenesis.10,11 In particular, the apoptotic effect was related to caspase-3 activation7 or a caspase-independent pathway8 and up-regulation of p53 and Bax.12 The anti-tumor effects of doxycycline have been reported in solid tumors, such as osteosarcoma,8 breast cancer,7 prostate cancer,7 and renal adenocarcinoma.14 Moreover, Iwasaki et al even proposed an antileukemic effect of doxycycline. Nevertheless, further clinical trials and pharmacologic investigations are indispensable to shed more light on the mechanism of action of doxycycline in the context of SMPTCL.

The exact nosologic classification of SMPTCL is still a matter of discussion.3 In particular, the striking difference between the worrying histopathologic findings on the one hand and the indolent clinical course on the other hand makes it difficult to classify SMPTCL definitively as benign or malignant. Some authors claim to use more descriptive terms like “cutaneous nodular proliferation of pleomorphic T lymphocytes of undetermined significance” rather than forcing SMPTCL into the one or the other category.3 Nevertheless, the clinical course of most published cases supports nonaggressive therapeutic regimens and long-term monitoring of patients with SMPTCL.

In conclusion, the present case provides strong evidence that doxycycline is a well-tolerated oral agent and has the potential to be of value in the therapy of SMPTCL.


