An ulcerated lesion due to HSV-2 infection with a CD56+ cell predominant inflammatory infiltrate

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KEY WORDS

herpes simplex virus, pseudolymphoma, natural killer cell lymphoma, lip, CD56, granzyme B

SUMMARY

CD56+ rich inflammatory infiltrates have been described in several cutaneous inflammatory conditions. However, CD56+ cells rarely account for more than 10% of the cells in such infiltrates. In certain conditions, such as insect bites or infection with herpes virus, CD56+ cells can be up to 43% of the cells in the infiltrate. This contrasts with what is observed in natural killer (NK)-cell lymphomas, which show a diffuse, atypical infiltrate in which most of the cells are CD56+. In this report, we describe a lymphocytic infiltrate in an ulcerated lesion on the lip of a 53-year-old man resulting from infection with herpes simplex virus type 2. CD56+ cells represented 80 to 90% of the infiltrate, showing atypical morphologic features, and clusters of CD56 positive cells were also observed.

Introduction

CD56+ rich cell infiltrates can be found in several benign conditions. Some cutaneous inflammatory diseases have been reported among these, such as lichen planus, lupus erythematosus (1), contact allergic dermatitis (2), and atopic dermatitis (3). Nevertheless, in these infiltrates, CD56+ cells rarely represent more than 10% of the infiltrate. Insect bites can sometimes induce infiltrates with up to 43% of CD56+ cells (4). It has also been described how infection with herpes-family viruses can induce pseudolymphomatous infiltrates that are rich in CD56+ cells (up to 25% of the cells in the infiltrate) (5).

In this report, we describe a case of a pseudolymphomatous inflammatory infiltrate with atypias and many CD56+ cells, which represented 80 to 90% of the infiltrate. Taken together, the topographic, morphologic, and immunophenotypic features create serious difficulties in the differential diagnosis with a natural killer (NK)-cell lymphoma.

Case Report

A 53-year-old male patient came to our office complaining of an ulcer on the oral mucosa of 10 days' duration. He said that the lesion started as a small erosion, with a very painful bullous stage, and it was currently a painless ulcer.

The examination revealed a 2 cm ulcer on the posterior fold of the upper lip that was firm and painless,

with a necrotic appearance and edematous mucosa around it (Fig. 1, top). There were no other lesions in the oral cavity, pharynx, or laryngeal mucosa.

A biopsy was performed and an initial treatment with mouthwash consisting of oral povidone-iodine solution, amoxicillin-clavulanic acid (875 mg/8 hours for 10 days), and ibuprofen (600 mg/8 hours for 7 days) was used. A microbiologic culture from the exudate of the ulcer was positive for common bacteria of the upper respiratory tract. Laboratory serology was negative for toxoplasmosis, syphilis, and tularemia.

The biopsy showed an ulcer with an intense diffuse lymphocytic infiltrate (Fig. 2, top left). The infiltrate showed many atypical cells with large nuclei, many of

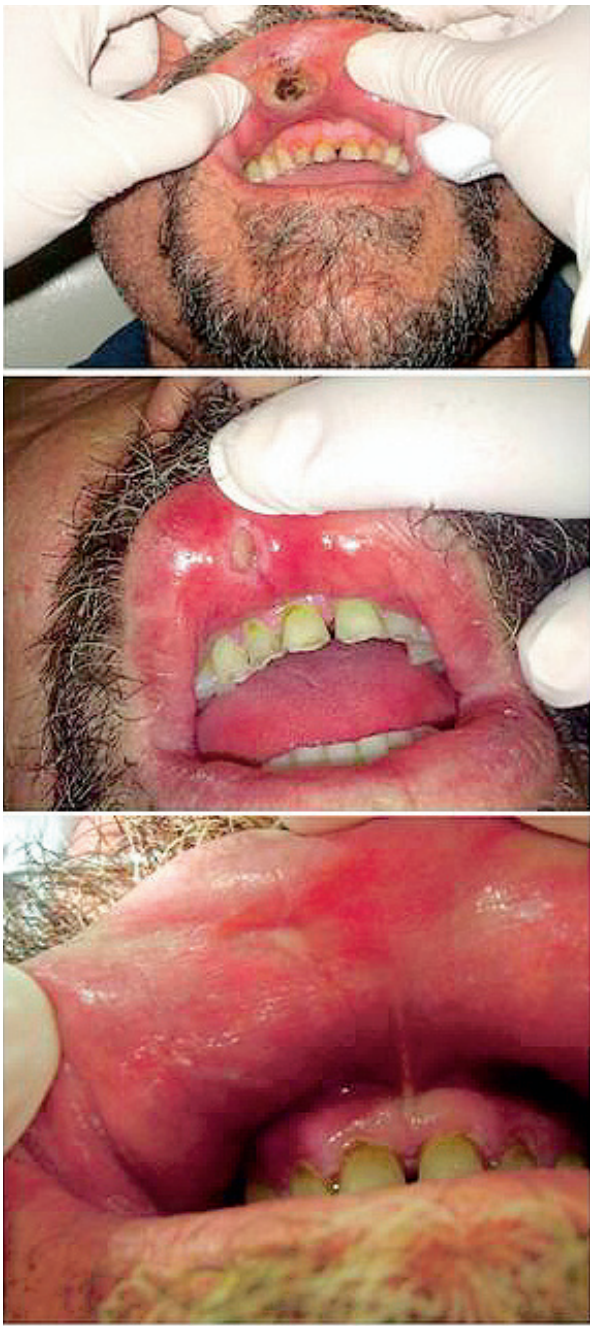

Figure 1. Clinical appearance of the lesion when the patient first came for examination (top), 12 days later (middle), and 17 days later (bottom), showing spontaneous regression of the lesion.

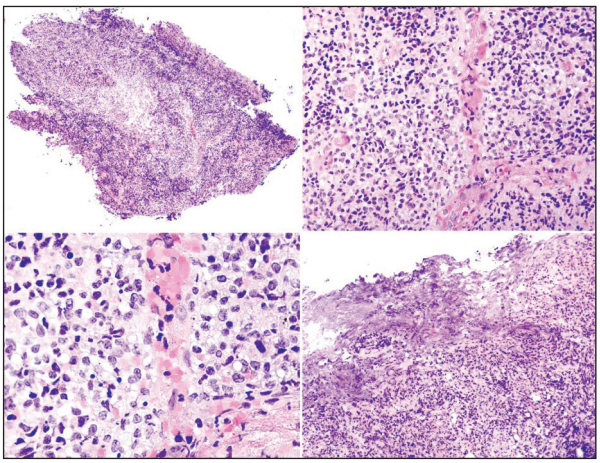

Figure 2. Biopsy of the ulcerated lesion, showing a diffuse lymphocytic infiltrate (top left). The lymphocytic cells were atypical (top right), and many had a wide nucleus with prominent nucleoli (bottom left). The epithelium was not preserved on the surface (bottom right) and no viral inclusions were observed.

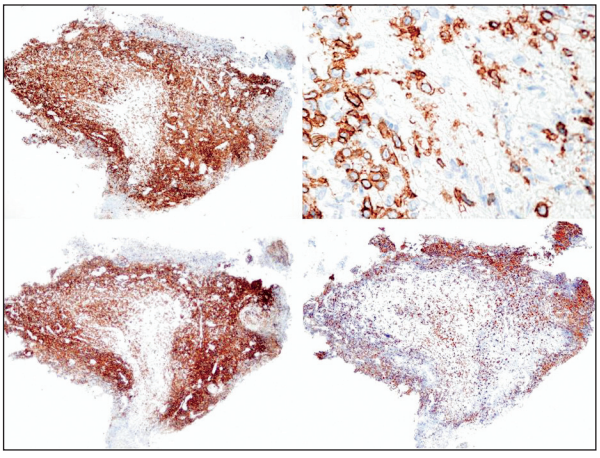

Figure 3. The lymphocytic infiltrate showed strong cytoplasmic expression of CD3 (top left and right) and CD8 (bottom left). A moderate amount of CD68+ histiocytes was also observed (bottom right).

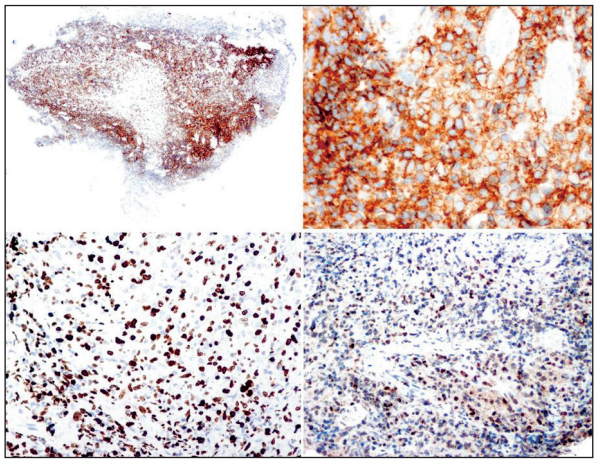

Figure 4. The infiltrate mainly consisted of CD56+ cells (top left). The latter were arranged in clusters (top right). The proliferation rate was very high (bottom left). Immunostaining for herpes simplex type 2 was positive (bottom right).

them with one or several prominent nucleoli (Fig. 1, top right and bottom left). There were no remains of epithelium covering the biopsy (Fig. 1, bottom right) and viral inclusions were not observed. There were no signs of angiodestruction by the infiltrate.

The immunohistochemical study demonstrated cytoplasmic expression of CD3 by most of the cells in the infiltrate (Figure 3, top left and right). These cells were CD20−, bcl-2+, bcl-6−, CD5+, CD43−, CD21−, S100−, CD34−, CD10−, CD23−, MUM-1−, CD4−, CD7−, CD30−, CD2+, myeloperoxidase−, CD57−, p53−, and cyclin D1−. A moderate amount of CD68+ histiocytes were also seen (Fig. 3, bottom right). Latent membrane protein (LMP)-1 immunoexpression was not observed and the test for the Epstein-Barr virus (EBER) using peptide nucleic acid probe/fluorescence was negative.

The infiltrate was rich in CD56+ cells. These represented 80 to 90% of the infiltrate and clusters of positive cells were also observed (Fig. 4, top left and right). The proliferation rate was high (about 70%; Fig. 4, bottom left). Granzyme B was expressed by 10% of these cells. Immunohistochemical staining for herpes simplex virus (HSV) type 1 was negative, but the one for HSV type 2 was positive (Fig. 4, bottom right).

Twelve days later, the lesion had mostly regressed although a small ulcer was still present (Fig. 1, middle). Treatment with ciprofloxacin was recommended (500 mg/12 hours for 7 days). After 17 days, the lesion had completely regressed, leaving a scarred zone (Fig. 1, bottom). The patient was asymptomatic.

Discussion

CD56+ cells can be found in benign lymphocytic infiltrates, such as those in lichen planus or lupus erythematosus (1). However, in such infiltrates, CD56+ cells represent about 0.1% (rarely more than 9%) of the infiltrate (6). This contrasts with natural-killer (NK)-cell lymphomas, in which CD56+ cells are the main component of the infiltrate (7), showing diffuse immunostaining (1). Nevertheless, in 2006, Leinweber et al. published a series of 65 patients with herpes virus infection (herpes simplex, herpes varicella/zoster) with pseudoinflammatory atypical lymphocytic infiltrates (5). Among these cases, 16 (24.61%) showed CD56+ cells in the infiltrate. Of these, in eight cases (12.30%) the CD56+ cells were scattered, up to 5%; in the other eight cases (12.30%), CD56+ cells represented between 5 to 25% of the infiltrate (in one case, clusters of positive cells were observed). CD56 testing was not performed in the rest of the cases, which means that in none of these cases was the infiltrate of CD56+ cells higher than 25% of the cells (5).

There are other examples of benign reactive inflammatory infiltrates secondary to insect bites, in which CD56+ cells can represent up to 43% of the infiltrate in the biopsy (4), and up to 50 to 60% of the peripheral blood mononuclear cells (8). This condition has been referred in the literature as hypersensitivity to mosquito bite-NK disease (8).

In the current case, the infiltrate consisted mostly of atypical CD56+ cells, with a high proliferation rate and with clusters of CD56+ cells. In view of these features, the main differential diagnosis was NK-cell lymphoma, which has a dismal prognosis (9, 10). The oral mucosa is not at all a rare location for this type of lymphoma (8, 9).

Testing negative for Epstein-Barr virus is always a factor that should make one doubt a diagnosis of nasal-type NK-cell lymphoma. LMP-1 is frequently expressed by NK-cell lymphomas (11) and positivity for EBER by in-situ hybridization is considered by some as a very important diagnostic clue (12). Chan et al. claimed that, "if only the nasal-type NK/T-cell lymphomas are considered, the positivity rate is 100%," (13), also clarifying, however, that "studies in Caucasian populations ... also support a strong although not invariable association with EBV" (13).

A clinical history of spontaneous remission is, obviously, a solid argument in favor of the benign nature of the infiltrate, although some cases of post-biopsy regression of NK-cell lymphomas have been described (12). In this context, there is a very interesting report on the spontaneous regression of an NK-cell lymphoma of the right periocular skin that started as itching, swelling, and erythema (14). The authors did

not test for HSV but Epstein-Barr virus was positive. However, the favorable progress (spontaneous regression in only two months) as well as the area involved (periocular) somehow suggests the possibility of an infection by the herpes virus family. Our case is an example of the fact that such a possibility has to be considered, even in dense infiltrates consisting mainly of CD56+ cells.

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