Cutaneous Presentation of Plasmablastic Lymphoma in a Patient with HIV Infection

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To the Editor:

Plasmablastic lymphoma (PL) is an uncommon variant of diffuse large B-cell lymphoma first described by Delecluse et al in 1997. It tends to be located in the oral cavity of patients with human immunodeficiency virus (HIV) infection. PL is highly malignant, and Epstein-Barr Virus (EBV) is believed to be implicated in its pathogenesis. The cells have an immunoblastic appearance, and are characterized by the loss of mature B-cell antigens, such as CD20, and the acquisition of plasma cell markers, such as CD38 and CD138. Treatment includes chemotherapy and highly active antiretroviral therapy, but response rates are low.

The patient was a 43-year-old woman referred to us for evaluation of painful progressive nodular lesions. Examination of the patient revealed firm subcutaneous nodules of between 1 cm and 3 cm in diameter on the trunk and lower limbs (Figure 1), adherent to the deep planes, and with a violaceous contusiform appearance of the overlying skin.

Relevant details of the patient’s history include previous parenteral drug use, hepatitis B virus (HBV) (surface antigen positive), hepatitis C virus (HCV), and HIV (stage B3) infection; she was on treatment with methadone and antiretroviral therapy (tenofovir, lamivudine, ritonavir, and atazanavir).

Blood tests included complete blood count, coagulation studies, biochemistry, serology, and tumor markers. The important results were CD4 counts of 377 cells/µL, abnormal liver function (aspartate aminotransferase, 87 U/L; alanine aminotransferase, 78 U/L; alkaline phosphatase, 177 U/L; and γ-glutamyltransferase 89), elevated β2-microglobulin of 4184.5 mg/L, and serological confirmation of HIV, HBV, and HCV infection, and markers for past infection by EBV.

Biopsy revealed the presence of a diffuse hypodermic tumor infiltrate made up of lymphoplasmacytoid cells with marked pleomorphism and numerous macrophages (Figures 2 and 3).

Immunohistochemistry was negative for CD20, multiple myeloma-1, B-cell lymphoma-6, CD3, terminal deoxynucleotidyl transferase, and Human herpesvirus (HHV)-8. However, tumor cells were positive for plasma cell markers such as CD138, and there was a high proliferation index. The Epstein-Barr virus encoded RNA (EBER) marker of EBV was positive using in situ hybridization techniques. A diagnosis of PL was made based on these results.

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A study of disease extension was requested, including a whole body computed axial tomography that confirmed tumor infiltration of the spleen, lymph nodes, and kidneys. The study was completed with a bone marrow aspiration and biopsy that showed reactive plasmacytosis and normocellularity in the three cell lines, ruling out tumor infiltration. The lymphoma was classed as stage IV-A.

Chemotherapy was started with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), and prophylactic intrathecal chemotherapy was also given. However, the patient died after the first cycle due to treatment-related complications.

According to the WHO-EORTC classification, PL is a diffuse large B-cell lymphoma with terminal differentiation. In 1997, Delecluse et al described a series of 16 patients with oral PL; 15 were HIV-positive men, and 11 were homosexual. Morphologically, the tumor presented characteristics of diffuse large B-cell lymphoma, but proved negative for the leukocyte common antigen and for CD20. Meanwhile, there was very clear presence of plasma cell markers, such as CD38 or CD138. Finally, recent studies indicate that large B-cell lymphomas with terminal differentiation could include a greater number of diseases than was initially thought; these diseases have different clinical-pathologic and phenotypic characteristics and include “buccal mucosa” type PL, PL with plasmacytoid differentiation, and PL secondary to multiple myeloma or plasmacytoma, among others.

Pathologic study characteristically reveals a proliferation of large, round or oval B lymphocytes with a large volume of eosinophilic cytoplasm and an eccentric nucleus with a prominent nucleolus. Macrophages are usually present, producing a “starry sky” appearance, and there is a high mitotic rate. Immunohistochemical analysis is positive for plasma cell markers such as CD38 and CD138.

The pathogenesis of PL is also associated with EBV (latency type 1 pattern), and positive results are commonly found for virus markers such as latent membrane protein, or EBER.

Initial studies on HHV-8 involvement in PL pathogenesis have been inconclusive, and it is currently considered to be a coincidental infection.

PL is highly malignant and prognosis tends to be poor despite chemotherapy. The most common chemotherapeutic regimen is CHOP; this achieves the best response rates. Recently, complete remission from cutaneous PL was reported in a patient with HIV infection who was treated with CHOP chemotherapy in association with highly active antiretroviral treatment.

Finally, recent studies indicate that large B-cell lymphomas with terminal differentiation could include a greater number of diseases than was initially thought; these diseases have different clinical-pathologic and phenotypic characteristics and include “buccal mucosa” type PL, PL with plasmacytoid differentiation, and PL secondary to multiple myeloma or plasmacytoma, among others.

References
To the Editor:

Ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome (MIM 129900) is the most common of a heterogeneous group of hereditary diseases in which ectodermal dysplasia and facial clefting coexist. Ectodermal dysplasia is defined as the abnormality of 2 or more organs of ectodermal origin, including hair, teeth, nails, sweat glands, external ear, cornea, conjunctiva, tear ducts and glands, and central nervous system. The 3 most important syndromes with associated ectodermal dysplasia and facial clefting are EEC syndrome, Rapp-Hodgkin syndrome—ectodermal dysplasia, cleft palate or lip, high forehead, midfacial hypoplasia, and small mouth (MIM 129400)—and Hay Wells or ankyloblepharon-ectodermal dysplasia-clefting (AEC) syndrome (MIM 106260).1,2 The apparent origin of this type of disease lies in mutations of the region of chromosome 3q27 that codes for protein p63—a homolog of the tumor suppressor p53—that regulates ectodermal development.3,4

We present the case of a 36 year-old man who was seen for a 3-month history of lesions at the corners of the mouth. Examination of the skin revealed some slightly excrescent, erythematous lesions associated with fissures at both oral commissures (Figure 1). Above the lips, superficial scars ran up on each side to the nasal vestibules.

General physical examination revealed malformations of both hands and feet, with absence of some of the central digits, a midline cleft, and fusion of some of the remaining digits, giving the appearance of “lobster claw” hands and feet (Figures 2 and 3). In addition, there was severe xerosis of the trunk and extremities and the hair was fine and blond. Intense bilateral conjunctival injection was also evident.

When the patient was asked about the lesions he reported no relevant dermatologic family history, only congenital malformations of the extremities. He had also undergone surgical intervention as a child for cleft lip and palate present at birth. In recent years he had been followed up in various ophthalmology departments for blepharoconjunctivitis, recurrent eye infections, trichiasis, and entropion, for which he had received treatment with artificial tears, corticosteroids, and ophthalmic antibiotics on many occasions.

The lesions at the oral commissures were diagnosed and treated as angular cheilitis in the context of a patient with EEC syndrome.

EEC syndrome is a rare congenital disease of autosomal dominant transmission, first described by Eckholdt and Martens in 1804.5 In 1970, Rüdiger introduced the acronym EEC (Ectrodactyly-ectodermal dysplasia-clefting), the current name for the syndrome. Patients affected by EEC syndrome characteristically present ectrodactyly (84% of cases)—also known as “lobster claw” hands and feet—which is caused by abnormal development of the hands and feet with an alteration of the central axis of the digits, absence of digits, a deep midline cleft, and fusion of some of the remaining digits.6 There may also be
abnormalities of the teeth and hair: hypoplastic or absent teeth, or early loss of the permanent teeth due to caries secondary to hypoplasia of the enamel (77% of patients), cleft lip or with or without cleft palate (68% of cases), and abnormalities of the lachrymal system (59% of cases). All of these were present in our patient. Abnormalities of the lachrymal system consist mainly of atresia of the tear duct and aplasia of the Meibomian glands, with defects in the tear film leading to epiphora, dacrocystitis, blepharitis, blepharoconjunctivitis, recurrent infections, corneal scarring, and deteriorating vision.6,7 Other less common features include abnormalities of the genitourinary system (hydronephrosis, chronic pyelonephritis, vesicoureteric obstruction, renal duplication or duplication of the collecting system, cryptorchidism, and hypospadias), conductive deafness, facial dysmorphism (broad nasal bridge, mandibular hypoplasia, and pointed chin), strabismus, recurrent respiratory infections, choanal atresia, short stature, and mental retardation.3,8,9

From a dermatological point of view, patients with EEC syndrome have fine, dry, blond hair, with the occasional presence of pili torti (twisted hair) and uncombable hair syndrome. Patients with ectodermal dysplasia and cleft palate can also present dermatitis and folliculitis of the scalp.1 Other dermatological abnormalities include dry skin, dermatitis at various sites, hypopigmentation, increased numbers of nevocellular nevi, hyperkeratosis of the palms and soles, and nipple abnormalities.1,3,8,9 We also observed angular cheilitis in this patient—a finding previously described by other authors.3 These lesions could be caused by the excess of saliva in the area as a result of anatomical changes secondary to the corrective surgery for the cleft left lip and palate, though bacterial or fungal agents could also be involved.

Although many published reports of the syndrome are of sporadic cases with no family history, prenatal detection of specific chromosomal abnormalities of this type of syndrome marks an important step forward for those patients wishing to have children. Prenatal detection of abnormalities of the p63 gene of chromosome 3 has already been used successfully, and healthy children have been born to parents with EEC syndrome.4,10 Management of these patients must be multidisciplinary. This should start with the surgical correction of defects that could cause a functional deficit, such as problems of phonation and hearing due to cleft palate, difficulties walking or handling objects due to ectodactyly, and abnormalities of the genitourinary system. Odontologic follow-up is also essential, with the correction of poor dental occlusion and caries, and the insertion of implants where necessary. Artificial tears and topical antibiotics may be required to avoid ocular problems, although the onset of ocular complications is sometimes insidious and may require other techniques in order to avoid problems such as entropion or trichiasis.

References

To the Editor:

A new form of comedones, known as childhood flexural comedones, has recently been reported.1 The authors described the development of comedones in the large skin folds during childhood, in which the comedones had 2 orifices connected via a thin layer of epidermis. No predominance in either sex has been reported. In most cases, the patients consulted for another condition and the comedones were an incidental finding. The lesions were usually solitary, unilateral, and located in the axillae.

Since this entity was first defined, we have seen 3 patients with lesions consistent with those described. A 5-year-old boy was seen for multiple comedones with double orifice in the axillae that had been present for 9 months (Figure). A soft, white, keratinous material was expressed from 1 of the larger, cystic lesions. A 25-year-old man, who consulted for severe acne, presented numerous comedones with double orifice on the neck and back from childhood. A 40-year-old woman, who had experienced polymorphic acne mainly on the face during adolescence, presented comedones with double orifice on both sides of the neck from childhood. None of the patients were aware of any other cases of flexural comedones in their families.

The appearance of comedones is usually related to acne, hidradenitis suppurativa, chronic sun damage, or other types of cutaneous damage.2 It can also occur after molluscum contagiosum infection.3 The site of childhood flexural comedones, which present particularly in the axillae and occasionally also in the groin, indicate that this entity could be related to hidradenitis suppurativa. The 2 adult patients described, who presented abundant comedones with double orifice on the back and neck, had developed severe acne during adolescence. This suggests that childhood flexural comedones could be related to the development of acne or hidradenitis suppurativa during adolescence or adulthood. These observations also indicate that childhood flexural comedones may persist into adulthood and may be found along with comedones with double orifice at different sites in the skin folds, as well as on the back.

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Flexural Comedones

G. Pitarch, A. Pitarch, and J.M. Sánchez-Motilla
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Figure. Comedones with double orifice, with a cystic lesion.

Unilateral Multiple Facial Angiofibromas: Description of a New Case

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To the Editor:

Tuberous sclerosis, also called tuberous sclerosis complex (TSC),1 is a rare multisystem genetic disease that causes benign tumors in the brain and other vital organs, such as the kidneys, heart, eyes, lungs, and skin. The prognosis of the disease is determined by renal manifestations, in which the appearance of renal angiolipomas causes retroperitoneal bleeding and progressive renal failure, the main causes of death in these patients.1

Bilateral multiple facial angiofibromas are the most common dermatologic manifestation of TSC and are considered a major criterion in establishing the diagnosis.1 The unilateral presence of facial
angiofibromas is rare, however, and only 14 cases have been published in the literature (Table).2-12 Other cutaneous manifestations are hypomelanotic macules, connective tissue hamartomas or nevi, and periungual or subungual fibromas. We present a new case of unilateral multiple facial angiofibromas with no other manifestations of TSC.

Our patient was a 40-year-old woman with a personal history of traumatic cataract in the right eye and appendectomy. She is currently being monitored by the neurology department for multiple sclerosis treated with AM3 (Inmunoferon). She consulted for the progressive appearance of completely asymptomatic, small papular lesions located in the left nasolabial crease that had been slowly, but steadily, growing since she was 15 years old. These lesions had been treated on various occasions by her primary health care physician with keratolytics, but with no apparent clinical improvement, hence her referral to our department. She had no personal or family history of any dermatologic, neurologic, renal, or cardiac disease, but did mention that a brother occasionally presented epileptic seizures of unclear etiology. Her parents were not consanguineous. The physical examination revealed multiple flesh-colored dome-shaped papules of 2 to 4 mm in diameter, randomly distributed, but primarily located in the left nasolabial crease, without crossing the midline (Figure 1). The remaining physical examination, including a comprehensive neurologic examination, was normal. Examination under Wood light did not show any hypopigmented lesions, and no ungual lesions were observed.

A histopathologic study of 1 of the cutaneous lesions confirmed the clinical suspicion of facial angiofibroma, revealing perivascular fibrosis associated with angiomatous hyperplasia (Figure 2). All imaging tests performed by the neurology department were carefully reviewed and, because the physical examination was strictly normal, no other additional tests were requested. We recommended carbon dioxide laser treatment, which was refused by the patient; she is currently attending periodic follow-up visits.

**Table. Case Reports of Unilateral Multiple Facial Angiofibromas Published to Date**

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<tr>
<th>Case No.</th>
<th>Year Published</th>
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Abbreviations: FA, facial angiofibromas; F, female; L, left; M, male; R, right.

**Figure 1.** Multiple small dome-shaped papules located in the left nasolabial crease, without crossing the midline.
TSC is a genetic disease of highly variable phenotype, characterized by the triad of mental retardation, epilepsy, and facial angiofibromas. It is presently considered a hamartomatous process characterized by a cell proliferation, migration, and differentiation disorder inherited as a dominant autosomal trait with variable penetration, although 60% to 70% of cases are sporadic. These sporadic cases represent new spontaneous mutations and, therefore, lack any prior family history of the disease as in our patient. The condition occurs as a result of mutations in the Tsc1 and Tsc2 genes. These determining genes have been identified on chromosomes 9q34 and 16p13.3.13

Bilateral multiple facial angiofibromas, formerly and incorrectly known as sebaceous adenomas, are a major criterion for diagnosis of TSC, but have been found in patients with type 1 multiple endocrine neoplasm and type 1 neurofibromatosis. The condition begins to develop in the mid-facial area during childhood (age 4-10 years) and affects 80% to 90% of patients with TSC, manifesting clinically as erythematous dome-shaped papules with a smooth, glossy surface. These lesions are composed of vascular and connective tissue, and although pathognomonic of TSC, are not very useful for early diagnosis because they appear in late childhood. The unilateral presence of these facial angiofibromas is rare: only 14 cases have been reported in the literature (Table), 8 of them with no other criteria of TSC. Our case represents an addition to this second group. However, the remaining 6 patients with unilateral facial angiofibromas presented other clinical findings that support the TSC diagnosis, such as hypopigmented macules, poliosis, amaurosis, and renal angiolipomas.

The significance of the unilateral development of facial angiofibromas has remained uncertain over the years. The first cases described were attributed to the various forms of expression of TSC, but they were later considered 1 of the first clinical signs of TSC. At present the condition is considered a segmental, genetically well-defined form of TSC caused by germline mosaicism. The presence of late postzygotic somatic mutation during embryonic development may be responsible for this mosaicism and would explain why only 1 segment of the body surface is affected.

Facial angiofibromas are an unsightly blemish on the face, with occasional episodes of bleeding and skin infections (in vegetating lesions, due to difficulty with hygiene). Various therapeutic measures, such as resection, cryosurgery, curettage, dermabrasion, carbon dioxide laser, argon laser, and pulsed diode laser have been recommended. Carbon dioxide laser has been successfully used to treat these lesions, although one of the most important problems is long-term recurrence because the lesions cannot be permanently removed, most likely due to their nature.

Early diagnosis of these segmental forms of TSC is important and, although the type of diagnostic examination and genetic counseling to be undertaken in patients with unilateral facial angiofibromas is unclear, like other authors, we believe that regular follow-up is essential. Such follow-up will detect any tumor growth or other complications and permit adequate therapeutic measures to be taken.

References

12. Hall MR, Kovach BT, Miller JL. Unilateral facial angiofibromas without other evidence of tuberous sclerosis:
Pale Orange Perifollicular Halo as a Dermatoscopic Sign in Scurvy

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To the Editor:
The cutaneous lesions of scurvy have traditionally been described as disseminated purpura, follicular keratotic papules, and “corkscrew” hair.1-3 The usual dermatoscopic findings have been described as follicular hyperkeratosis, bleeding, and corkscrew hair.4 Our patient with chronic scurvy presented peculiar scurvy-related findings in the dermatoscopic examination.

A 68-year-old man with a history of alcoholism and no teeth, who had been following a diet consisting solely of plain cakes for quite some time, came to the emergency department of our hospital. He presented considerable deterioration in his overall condition from 2 months previously as well as asthenia, anorexia with significant weight loss, and progressive tendency to be bed-ridden, pain and swelling in the right knee, and violaceous cutaneous lesions on the legs and abdomen (Figure 1). His personal history included several episodes of hemarthrosis and flare-ups of hematuria in the previous 2 years that had not been specifically diagnosed. Dermatoscopy of the cutaneous lesions revealed a pale orange perifollicular halo surrounded by another peripheral hemorrhagic violaceous halo, along with “corkscrew” hair and follicular hyperkeratosis (Figure 2). A skin biopsy showed a ringlet-like hair shaft sectioned at different levels inside the follicle, compact perifollicular fibrosis, and extravasated erythrocytes in the dermis, but not in the perifollicular fibrotic area mentioned above (Figure 3).

Figure 1. Note the large violaceous lesions, follicular hyperkeratosis, and coiled hairs observed in our patient.

Figure 2. In addition to “corkscrew” hair, the dermatoscopic image showed a pale orange perifollicular halo, surrounded by violaceous lesions.
Because scurvy was suspected, plasma ascorbic acid levels were measured and found to be noticeably low (<0.1 mg/dL; normal range, 0.2–0.4 mg/dL), thereby confirming the diagnosis. The patient responded extremely well to oral treatment with vitamin C and nutritional supplements of fruits and vegetables; the skin lesions disappeared within 15 days and his overall health improved noticeably.

The peculiar pale orange halo observed on dermatoscopy could be explained as the result of the usual changes observed in the violaceous lesions once the extravasated erythrocytes began to be reabsorbed. Such reabsorption might start near the follicle, explaining the presence of the orange halo as a temporary finding within a dynamic process. Against this explanation was the fact that the patient had still not started treatment or experienced clinical improvement as a result. We felt that a correlation between the dermatoscopic image and histopathologic findings was more likely. The perifollicular fibrosis observed in our patient would have rejected or prevented erythrocyte accumulation in the area and both factors (fibrosis and absence of erythrocytes) would explain the pale orange halo mentioned. Beyond the fibrosis area, the dermal collagen would be looser and so allow erythrocytes to accumulate, producing hemorrhagic lesions at the periphery of the pale orange area.

We therefore believe that this dermatoscopic observation is not without importance, but could be correlated with the histopathologic findings. If confirmed, the observation could allow chronic and acute scurvy to be distinguished through a clinical sign. There is no reason why acute scurvy would be associated with such a halo, since the perifollicular fibrosis that determines this dermatoscopic sign would not have developed. However, more observations are needed to confirm the validity of this observation.

References
delimited, nonencapsulated lesion centered in the dermis and lined with nonulcerated epidermis, that also presented moderate cell proliferation composed of large histiocytic cells with abundant eosinophilic cytoplasm of “ground glass” appearance and rounded or oval nuclei with prominent intensely eosinophilic nucleoli (Figure 2). No type of atypia, necrosis, or mitosis was observed. The oncocytic cells were accompanied by an inflammatory infiltrate of lymphocytes, eosinophils, and polymorphonuclear neutrophilic leukocytes. Immunohistochemistry was positive for factor XIIIa, CD68, vimentin, and 1-antitrypsin. S-100 staining was negative. Since his first visit, the patient has remained asymptomatic and presented no signs of relapse at the time of writing.

Solitary reticulohistiocytoma was first described by Zak in 1950. It is characterized by a usually asymptomatic, well-delimited papule or nodule with a smooth surface, of 0.3 to 2 cm in diameter. The lesions are of firm consistency and variable color, ranging from yellow to reddish-brown. They can appear on any part of the body. Some authors report that the lesions are less common on the face and the fingers or toes, unlike multicentric reticulohistiocytosis, although others have observed it most often on the face and neck. It is more common in young adults and slightly more predominant in men. The development of reticulohistiocytosis in areas of traumas has been described, but most cases appear spontaneously. The lesions are benign, self-limiting, and rarely recur after surgical removal.

Histologically, the lesions are characterized by a mixed infiltrate of eosinophilic epithelioid histiocytes with abundant glassy cytoplasm, multinucleated cells, and other inflammatory cells. The infiltrate reaches the reticular dermis, and frequently the subcutaneous tissue. Isolated Touton-type cells with lipids in the interior are occasionally observed. The epidermis tends to be somewhat hyperplastic and hyperkeratotic, and ulceration is rare. In the immunohistochemical study, the cells are positive for factor XIIIa and CD68 but negative for CD1a and CD34. S-100 staining tends to be negative, although isolated cases of positive findings for this marker have been described. Clinical differentiation from other histiocytic and granulomatous processes, such as multicenter reticulohistiocytosis, is important due to the possibility of systemic involvement and associated risk of malignancy. Although solitary reticulohistiocytomas present similar histopathologic findings, they tend to have a higher neutrophilic and eosinophilic component in the infiltrate and the stroma tends to contain numerous fusiform cells, some of them xanthomized (Table). The lesion may also be difficult to differentiate clinically and histopathologically from solitary adult xanthogranuloma, although lipidized histiocytes and the presence of Touton-type cells in the latter are characteristic, with the accompanying mixed infiltrate having fewer eosinophilic cells. Rarely, a solitary reticulohistiocytoma may be confused clinically with another type of nonhistiocytic neoplasm. In our patient, the somewhat keratotic appearance of the surface and its crateriform shape were clearly similar to those of a keratoacanthoma,

Table. Clinical Characteristics and Laboratory Findings for the Various Forms of Reticulohistiocytosis

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<td>Number of lesions</td>
<td>Single</td>
<td>Multiple</td>
<td>Multiple</td>
</tr>
<tr>
<td>Distribution</td>
<td>Head and neck, trunk, legs</td>
<td>Diffuse</td>
<td>Limbs, face, mucosae</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Malignancy</td>
<td>No</td>
<td>No</td>
<td>Yes, 25%</td>
</tr>
<tr>
<td>Internal organ involvement</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Laboratory values</td>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>

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something not previously described in solitary reticulohistiocytoma or any other histiocytic process, except for 2 cases of benign fibrous histiocytomas in the facial region. The etiology of solitary reticulohistiocytoma is unknown. It is considered a reactive process, rather than a true neoplasm. Some authors advocate changing the name of this entity from reticulohistiocytosis, which they consider somewhat archaic, to solitary epithelioid histiocytoma, since it would more accurately reflect the cytology and immunophenotype of this entity.

References