Histoid leprosy with giant lesions of fingers and toes

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Histoid leprosy, a clinical and histological variant of multibacillary leprosy, may offer a challenging diagnosis even for experts. An 83-year-old woman presented with papular, nodular and tumor-like lesions of 3 years of evolution, affecting fingers, toes, hands, thighs and knees, and wide superficial ulcers in her lower calves. Cutaneous lymphoma was suspected. A biopsy of a nodule of the knee showed a diffuse dermal infiltrate with microvacuolated histiocytes, moderate numbers of lymphocytes and plasma cells. Cutaneous lymphoma was suggested. Immunohistochemistry (IHC) showed prominent CD68-positive macrophages, as well as CD3, CD8 and CD20 positive cells. Additional sections suggested cutaneous leishmaniasis. New biopsies were sent with the clinical diagnoses of cutaneous lymphoma, Kaposi’s sarcoma or lepromatous leprosy, as the patient had madarosis. These biopsies showed atrophic epidermis, a thin Grenz zone and diffuse inflammation with fusiform cells and pale vacuolated macrophages. Ziehl-Neelsen stain showed abundant solid phagocytized bacilli with no globii formation. Abundant bacilli were demonstrated in the first biopsy. Histoid leprosy was diagnosed. The patient received the WHO multidrug therapy with excellent results. We concluded that Ziehl Neelsen staining should be used in the presence of a diffuse dermal infiltrate with fusiform and vacuolated histiocytes, which suggests a tumor, and an IHC particularly rich in CD68-positive macrophages; this will reveal abundant bacilli if the lesion is leprosy. A good clinical pathological correlation is essential to establish a proper diagnosis and management of the patient.

Key words: Leprosy; leprosy, multibacillary; leprosy, lepromatous.

doi: http://dx.doi.org/10.7705/biomedica.v35i2.2562

Lepra histioide con lesiones gigantes de los dedos de manos y pies

La lepra histioide es una forma de lepra multibacilar de diagnóstico clínico e histológico difícil incluso para expertos. Una mujer de 83 años se presentó a consulta con pápulas, nódulos y tumores de tres años de evolución en los dedos de manos y pies, y en manos, muslos y rodillas, así como úlceras superficiales extensas en la porción inferior de las pantorrillas, ante lo cual se sospechó linfoma cutáneo. La biopsia de un nódulo de la rodilla mostró infiltrado dérmico difuso con histiocitos microvacuolados y algunos linfocitos y plasmocitos. Se sugirió la posibilidad de un linfoma cutáneo. La inmunohistoquímica demostró macrófagos prominentes positivos para CD68 y células CD3, CD8 y CD20. Con base en los cortes adicionales de la biopsia, se sugirió la presencia de leishmaniasis cutánea. Se tomaron nuevas biopsias con las sugerencias diagnósticas de linfoma cutáneo, sarcoma de Kaposi o lepra lepromatosa, pues la paciente presentaba madarosis. Estas mostraron epidermis atrófica, una delgada zona subepidérmica de colágeno denso y dermatitis difusa con células fusiformes y algunos macrófagos vacuolados. La coloración de Ziehl-Neelsen reveló la presencia de bacilos abundantes en los macrófagos, sin tendencia a formar globias. En la primera biopsia se demostraron abundantes bacilos. Se diagnosticó lepra histioide. La paciente recibió quimioterapia antileprosa (Organización Mundial de la Salud) con resultados excelentes. Se concluyó que un infiltrado dérmico difuso con histiocitos fusiformes y algunos vacuolados, que sugiere un tumor fusocelular, cuya inmunohistoquímica sea particularmente rica en células positivas para CD68, debe teñirse con Ziehl-Neelsen, lo que revelará abundantes bacilos si la lesión es de lepra. La adecuada correlación clínico-patológica es necesaria para establecer el diagnóstico y el manejo preciso del paciente.

Palabras clave: lepra, lepra multibacilar, lepra lepromatosa.

doi: http://dx.doi.org/10.7705/biomedica.v35i2.2562

Author’s contributions:
Gerzaín Rodríguez: Histopathological study of biopsies, design and writing of the paper, literature review
Rafael Henríquez and Shirley Gallo: Clinical study, control and treatment of the patient, review of manuscript and of literature
César Panqueva: Histopathological study of biopsies, review of manuscript and of literature
Case history

An 83-year-old woman presented with lesions of three years of evolution in the form of numerous papules, nodules and tumors on the dorsal surface of both hands and wrists, over the metacarpal-phalangeal joints, and on the dorsal surface of the digits (figure 1). Similar lesions were located over the distal phalangeal joints of toes (figure 1), on the skin of knees and on the lower third of the posterior face of the thighs (figure 1). The lesions were well circumscribed, with a thick border and a 1-4 cm diameter; some had a depressed surface and were ulcerated, hyperkeratotic and crusty (figure 1). A wide ulceration on the lower third of her left calf and confluent excoriated nodules on her right one were also visible (figure 1). Her general condition was good and she had only complained of frequent epistaxis during the previous two years. Her eight sons were also in good health and she did not report having any serious diseases before. Routine blood, urinalysis and lipid profile were normal.

The clinical findings were puzzling. A cutaneous lymphoma was suspected with vasculitis of the calves. Two biopsies were taken, one from the left knee and the other one from the border of the left leg ulcer. The first one was a 4 x 3 mm-skin cylinder with changes reported as suggestive of cutaneous lymphoma. Immunochemistry (IHC) was recommended. The leg skin biopsy showed a superficial ulcer bordered by moderate epidermal hyperplasia and dermis with granulation tissue, purpura and fibrosis without presence of tumor. The review of new sections from the first biopsy and the corresponding IHC showed scant lymphoid infiltrate without cellular atypia, CD3, CD8 and scant CD20-positive cells, and abundant CD68 and S100-positive cells (figure 2). No parasites were seen, but cutaneous leishmaniasis was suggested.

Two additional skin biopsies from different lesions far apart were then taken: one from the dorsal left hand and another one from the left knee. The suggested clinical diagnosis included cutaneous T cell lymphoma, Kaposi’s sarcoma and lepromatous leprosy, as the patient had alopecia in the outer third of eyebrows, although this was posed without much conviction.

These biopsies were studied with routine methods and given the possible presence of lepromatous leprosy, Ziehl-Neelsen stain was also used. The specimens were small skin fragments, with no hypodermis, covered by atrophic epidermis and with a dense macrophage dermal infiltrate with elongated or polygonal cells with or without slightly vacuolated cytoplasm, occasional plasma cells and a scant number of lymphocytes (figure 3). It was surprising to observe that both biopsies had abundant acid-fast bacilli with no tendency to form globii (figure 3). These changes were consistent with histoid leprosy. The revision of the first biopsy also showed abundant leprosy bacilli. No nerves were demonstrated in any of the biopsies, not even in sections stained with S100, and there were no signs of type 1 or 2 lepra reactions.

The bacilloscopy of the lesions showed a bacillary index of 4 and no granular forms. It was also positive in the smears from nasal mucosa, both ears and the left elbow, with a bacillary index lower to the one registered in the lesions.

The examination of the patient and the review of her clinical history did not reveal leprosy family contacts or with other leprosy patients. There was discrete excoriation of the nasal septum without perforation or any damage of the cartilaginous skeleton. There was a slight deformity and deviation of the nose to the right, and a small superficial ulcer on the right nasomalar sulcus, madarosis on both eyebrows

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Recibido: 30/09/14; aceptado: 18/12/14
Figure 2. A-B. First biopsy of an ulcerated lesion of the left knee. Diffuse inflammation with numerous lymphocytes. C. Lymphocytes and numerous vacuolated macrophages. Hematoxylin and eosin, 4X, 10X, and 25X.

Figure 3. A-B. Third biopsy of the left hand. Superficial specimen covered by atrophic epidermis and a diffuse dermal infiltrate with fusiform and discrete vacuolated cells. Hematoxylin and eosin, 2.5X, and 6X. C. Fusiform macrophages are predominant. Arrows point to some vacuolated cells. Hematoxylin and eosin, 40X. D. Huge amounts of acid-fast bacilli, isolated or forming groups without globii. Ziehl-Neelsen 60X.

and a papule on the right ear. The lesions were hypo or anesthetic, and both cubital nerves were slightly enlarged.

Multidrug treatment for leprosy was initiated with very good response and no leprosy reactions. Presently the patient has recovered from the disease. In conclusion, the proper clinic-pathological correlation allowed us to establish a difficult diagnosis, which on its turn led to a proper management and cure of the patient.

Discussion

Occasionally, leprosy is very difficult to diagnose, particularly in cases of histoid leprosy, which may be overlooked even by experts (1). When the clinical photographs of this patient were shown to a dermatologist, expert in leprosy, he claimed that: “These lesions cannot be of leprosy”. Initially, this possibility was not considered either by the physicians attending to the patient because her nodular and tumor-like lesions were not typical of leprosy.
The patient's characteristics sustaining a diagnosis of histoid leprosy included her good general condition, in spite of the profuse and chronic nodular and tumor-like lesions, well-delimited lesions with sharp borders on apparently normal skin and bony prominences, and the two skin biopsies showing diffuse macrophage inflammation with fusiform cells, admixed with some slightly vacuolated macrophages, both of them containing abundant acid-fast elongated intact bacilli with no granular forms and no tendency to form globii (1-9). Epistaxis is frequently described in histoid leprosy (6-11). Furthermore, positive bacilloscopies of nasal, ear and elbow smears are also seen in this type of leprosy (6,8,9,12). A unique finding in this case was the presence of nodules and tumors on fingers and toes. Leg ulcers are not characteristic of histoid leprosy. These findings show the mixed nature of lepromatous and histoid leprosy, the latter entity being considered as a frustrated form of the first (2-4,13), which, nevertheless, deserves its proper place in the classification of leprosy (9).

One of the initial skin biopsies taken from the border of an ulcerated lesion on the left hand showed discrete epidermal hyperplasia and a diffuse dermal infiltrate with a moderate amount of lymphocytes, which suggested the possibility of lymphoma, a diagnosis which was also proposed by the clinicians. Since this was a biopsy performed on the periphery of the lesion, it is possible to find numerous lymphocytes in this area of the lesion (4,5,14). The specimen submitted for IHC study had scant remaining tissue. It did not show any tumor, but a lesion rich in CD68 and S100-positive histiocytes, with scant CD3, CD8 and CD20-positive cells (figure 2). The possibility of cutaneous leishmaniasis was suggested although no amastigotes were seen, acknowledging that they are difficult to find in chronic lesions. The small and superficial biopsy did not allow suspecting leprosy.

To make a proper histopathologic diagnosis of histoid leprosy, a mandatory study of this disease (9,14), it is necessary to study a complete papule, nodule or tumor, which would show its circumscription and its expansive and not infiltrative character, as well as epidermal compression and atrophy (1,3,4,6,8,9,14). The periphery of the lesion may contain numerous lymphocytes and also pale vacuolated histiocytes, as was seen in this biopsy. In the new biopsies, sent with timidly suspected diagnosis of lepromatous leprosy because of the presence of madarosis, the Ziehl-Neelsen stain showed abundant leprosy bacilli, confirming the diagnosis of multibacillary leprosy; the global histological changes matched with those described for histoid leprosy (2,4,8,14,15), a diagnosis that had a satisfactory clinic-pathological correlation.

Histoid leprosy was described initially by Wade in the Philippines in 1963 (16) as a relapsing form of lepromatous leprosy in patients treated with dapsone monotherapy for long periods with partial or good control of the disease. It was considered as the result of dapsone-resistant bacilli (16), and it appears with cutaneous and subcutaneous papules, nodules and tubercles (from one to more than 100), and with plaques mainly over bone surfaces of elbows and knees (1,3,6-8). Nodules and tumor-like lesions appear very well defined, erythematous, firm, hypo or anesthetic over apparently normal skin and they measure from 0.5 to 5 cm in diameter (6-9,13). They may show superficial ulceration and some papules are centrally depressed or umbilicated, mimicking molluscum contagiosum (17). Lesions prevail on thighs, buttocks, arms, back, face, forearms and legs (1,6,8,9). Lesions on fingers and toes, as those found in our patient, have not been described before. Occasionally, mucosal lesions on the soft and hard palate, inferior lip and glans penis have been reported (18,19). Nasal perforation or destruction of nasal cartilage does not occur even in very long standing lesions (5,9), but epistaxis and nasal positive bacilloscopy have been demonstrated, as was the case in our patient (8). Madarosis, which is occasionally present (12,20), was a clue finding to deduce the right diagnosis in our case. Peripheral nerve enlargement, also a common finding (1,8,18), was slightly apparent in our case. Nodular swelling of cutaneous nerves is another presentation of histoid leprosy, sometimes as a relapse of lepromatous leprosy (21).

Histoid leprosy is more frequent among young men, with a male-female ratio of 6:1 in India (1,8,9), but it also occurs in children (22). Patients usually have a general good health, which was the case of our patient.

Histoid leprosy occurs:
1) as relapsing disease;
2) over lepromatous leprosy or other forms of multibacillary leprosy, or
3) de novo, without previous signs or leprosy treatment (1-3,6,9,11,23).

1) It appears as a relapsing disease in multibacillary patients following prolonged treatment with
Biomédica 2015;35:165-70

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dapsone or DDS. Usually, the treatment is incomplete and irregular, but it has also been detected after an adequate treatment and it may appear from 2 to 20 years after lepromatous leprosy has been cured (15). The fact that histoid leprosy has been reported following adequate multidrug treatment is especially noteworthy (24,25). It is commonly believed that histoid leprosy bacilli are resistant to DDS, and although this has been confirmed several times, there are other cases in which it has not happen or it has not been demonstrated (9).

2) This is the most frequent form of presentation (1). It appears over lepromatous leprosy plaques or non-treated borderline lepromatous leprosy. In a study this happened in 85% of the 40 patients in the sample.

3. It may also appear de novo, as the initial clinical presentation of leprosy. Papules and nodules appear upon apparently normal skin in cases with no previous history of leprosy treatment (1,8,11,23), as in our patient.

Wade emphasized that the patients did not present erythema nodosum leprosum, but this reaction does occur in histoid leprosy: It was detected in up to 40% of 40 patients in the above-mentioned study (3). It is suggested that erythema nodosum leprosum occurs in the evolution of lepromatous leprosy to histoid leprosy, but that it is uncommon when the latter is plainly (de novo) established (8,9,14).

Histopathological changes in histoid leprosy are characteristic: there is a dermal expansive infiltrate covered by thin, atrophic epidermis under which there is a thin Unna’s band. The infiltrate is diffuse, hypercellular, composed of elongated, fusiform macrophages; there may also be polygonal cells, but no foamy cells; pale vaculated histiocytes can be demonstrated at the periphery of lesions (1-4,8,9,13-15). Some plasma cells can be seen dispersed within the fusiform cells, a finding that we consider as a clue to differentiate this lesion from fusiform tumors. Ziehl-Neelsen staining shows abundant acid-fast bacilli within the macrophages, elongated, of uniform size, and with no granular forms (1-4,8,9,13,14). The morphology of the phagocytic cell is not disturbed by such a big amount of germs, which tend to follow the longitudinal axis of the macrophage and adopt the so-called “histoid habitus” (16). There is no tendency to form globii, but these may be present (1-4). Cutaneous appendages and nerves are pushed out by the infiltrate and can be seen in the periphery of the lesion. Nerves show the common changes seen in leprosy, which is a good aid to diagnose the disease.

The clinical differential diagnosis includes papular, nodular and tumor-like lesions such as in neurofibromatosis, which is rarely concomitant with histoid leprosy (26), xanthomas, common warts, molluscum contagiosum (17), keloids, Kaposi’s sarcoma (a diagnosis suggested in our patient), eruptive keratoacanthomas, diffuse cutaneous leishmaniasis, onchocerciasis, metastasis (20) and Mycobacterium avium intracellulare lesion in HIV patients (27).

Histologically, the main differentiation should be made with common lepromas, which are formed of foamy macrophages and have abundant globii, with nodular subepidermal fibrosis (4), with dermatofibromas and with neurofibromas, a diagnostic misinterpretation commonly made by general pathologists in histoid leprosy biopsies (9,13). A wide and deep biopsy, ideally including a complete papule, nodule or tumor, is of great help. Ziehl Neelsen or Fite-Faraco stains definitely confirm the multibacillary nature of the lesion.

The treatment is the recommended World Health Organization multidrug treatment for multibacillary leprosy, which offers very good results as was the case with our patient (9,25).

Histoid leprosy represents a challenge for leprosy elimination campaigns because of the usual delay in diagnosis, its difficult clinical and histopathological identification, its great bacillary index, the eventual resistance of the bacilli to DDS and the occurrence of lepromatous leprosy relapses manifesting as histoid leprosy after complete MDT (9,14,23,25).

Conflicts of interest
Authors declare they have none.

Financial support
Authors’ own resources and financial aid from the Universidad de La Sabana

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