Milroy Disease or Primary Congenital Lymphedema Associated With Invasive Squamous Cell Carcinoma☆

Enfermedad de Milroy o linfedema primario congénito asociado a carcinoma espinocelular invasor

To the Editor:

Milroy disease or primary congenital lymphedema was first described in 1892. It is characterized by congenital lymphedema of the lower limbs. Associations have been observed between chronic lymphedema and a number of neoplasms, including angiosarcoma, Kaposi sarcoma, lymphoma, basal cell carcinoma, melanoma, and squamous cell carcinoma (SCC).[1,2]

A 58-year-old man with a history of congenital lymphedema, with aplasia of lymph vessels in both lower limbs demonstrated on lymphoscintigraphy in childhood and a hereditary family history of the same disease (father), had undergone numerous operations to improve lymphatic circulation. He was seen in the dermatology department for a deterioration of the lesions that affected both lower limbs symmetrically and the genitalia since birth. In the pretibial region, the calves, and the dorsum of the feet, the patient presented papillomatous verrucous plaques, areas of fibrosis and atrophy, retracted scars, and small circular ulcers with erythematous borders and a seropurulent exudate. The thighs presented marked, hard edema, with surgical scars, and there was massive edema of the testicles that deformed the region, associated with verrucous plaques (Fig. 1, A and B).

A multilobulated tumor measuring 14 cm in diameter was observed in the left inguinal region. The exophytic tumor had a friable erythematous surface covered by fibrin (Fig. 2A). A poorly defined erythematous exophytic tumor with hyperkeratotic areas and elevated pigmented borders was observed on the shaft of the penis (Fig. 2B).

On a suspicion of SCC or angiosarcoma, incisional biopsies were taken from the lesions in the left inguinal region and on the penis, and computed tomography (CT) of the abdomen, pelvis, and lower limbs was requested.

Histopathology revealed a poorly differentiated, invasive squamous cell carcinoma with a thickness of 4.22 mm, Clark level V, with 11 mitoses per mm^2, and, on the penis, a well-differentiated invasive SCC with a thickness of 1.2 mm, Clark level IV, with 15 mitoses per mm^2. Neither tumor presented perineural or lymphovascular invasion or association with human papillomavirus (Fig. 3, A and B). On CT, numerous lymph nodes with a diameter less than 1 cm were visible in the mediastinum and more than 15 lymph nodes of up to 12 mm diameter in the right axilla. The patient was referred to another hospital where he has received chemotherapy with paclitaxel, cisplatin, and ifosfamide; he has completed 4 cycles but has shown no clinical or radiological improvement.

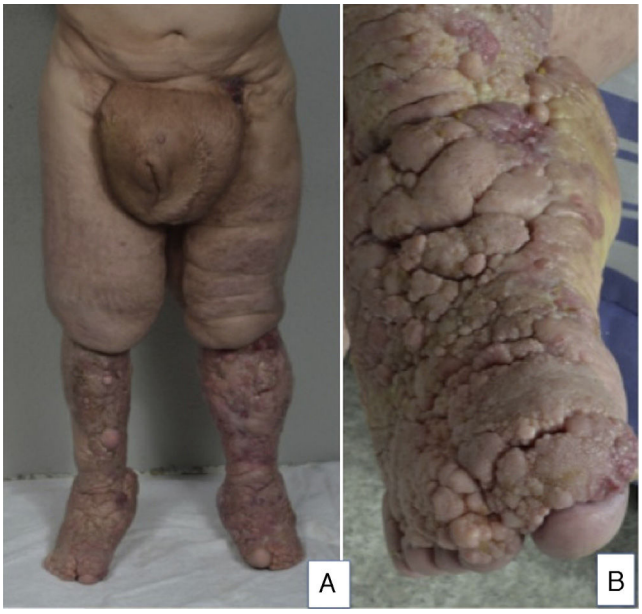

Figure 1 A, Marked bilateral lymphedema. B, Detail of the dorsum of the right foot.

Lymphedema is a progressive edema of the tissues secondary to a dysfunction of the lymphatic system. It can be primary or secondary. Primary lymphedema is due to abnormal development of the lymphatic system and the secondary form is due to trauma, lymph-node resection, tumors, or infections such as filariasis. Secondary lymphedema accounts for 99% of cases.[1–3]

Primary lymphedema is usually idiopathic, with no hereditary family history. The incidence is 1.15 per 100 000 population.[3] Non-idiopathic causes include a number of diseases with an autosomal dominant pattern of transmission, such as Milroy disease, which is characterized by congenital lymphedema of the lower limbs.[1–5] The locus has been mapped to 5q35.3 and the mutated gene is *FLT4*, which codes for endothelial growth factor receptor 3. It presents with lymphedema of the lower limbs affecting the dorsum of the feet, knees, and thighs; the edema has a woody texture.[4–7]

Diagnosis is made in patients with symmetrical bilateral congenital edema of the lower limbs, but other factors must be taken into account, such as a positive family history and mutation of endothelial growth factor receptor 3 (present in 42% of patients).[4]

The lymphedematous region becomes an immunocompromised territory due to altered migration of dendritic cells, T cells, and macrophages to the dermal lymph vessels.[7,8] One of the most common tumors to arise in Milroy disease is angiosarcoma (Stewart-Trevès syndrome), which, despite being more common in patients after surgery for breast cancer, has also been reported in lymphedema of the lower limbs. Other associated tumors are Kaposi sarcoma, lymphoma, basal cell carcinoma, melanoma, and SCC. The time over which the neoplasm develops can vary

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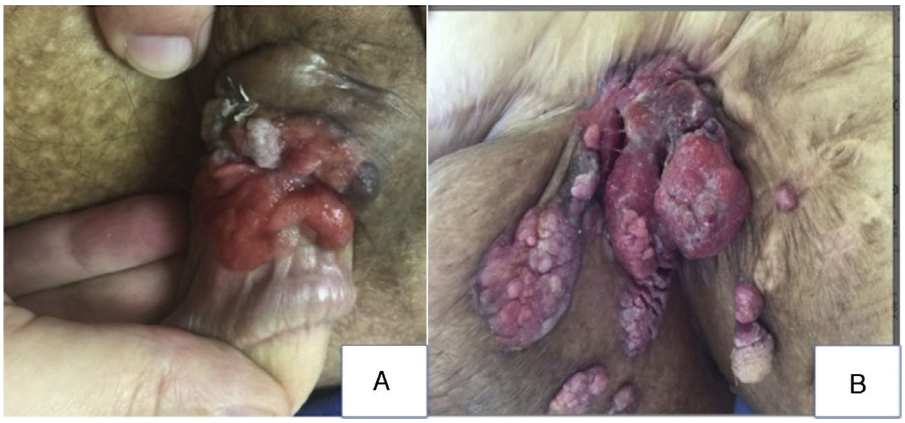

Figure 2 A, Tumor in the groin. B, Tumor on the shaft of the penis.

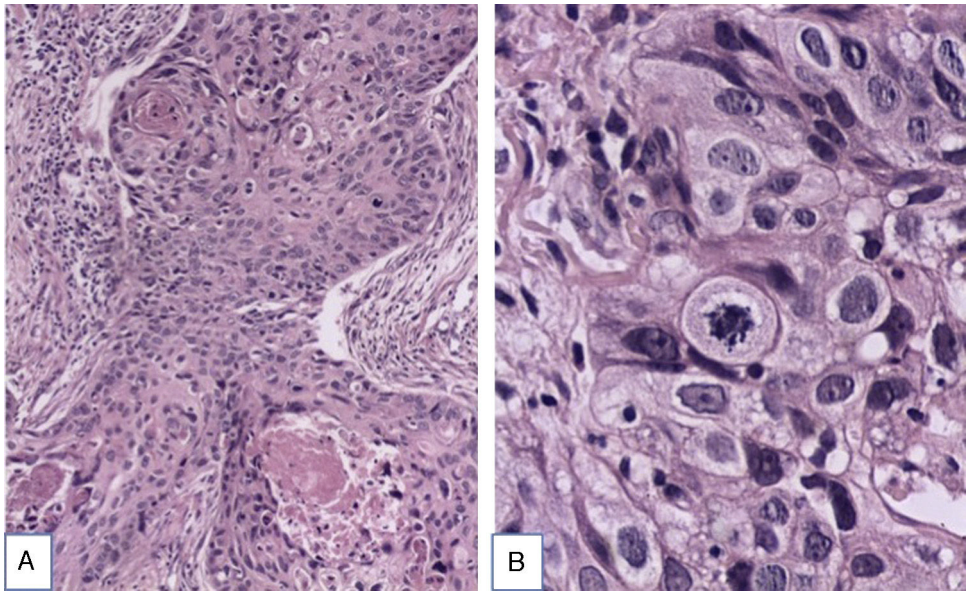

Figure 3 Histologic sections of skin showing the formation of squamous whorls and corneal pearls, large atypical keratinocytes with pleomorphic hyperchromatic nuclei and abundant eosinophilic cytoplasm, and atypical mitoses. Hematoxylin and eosin, original magnification A ×10 and B ×40.

from years to decades.[6–10] The most relevant risk factors for SCC in patients with primary lymphedema are common warts, angiosarcoma, widespread vitiligo, chronic ulcers, chronic verrucous hyperplasia, dystrophic epidermolysis bullosa, and a history of UV-B therapy.[9,10]

Only 15 cases of SCC associated with chronic lymphedema have been reported, and only 3 of these were associated with primary lymphedema. All these cases occurred in men. The mean age was 40.5 years and the most common site was on the lower limbs.[8–10]

The treatment of choice is resection of the tumor, combined with lymphadenectomy when lymph-node metastases are present. Adjuvant radiotherapy and chemotherapy may be administered.[10]

The importance of this case derives from the low frequency of these tumors in the context of primary lymphedema and the few cases reported in the literature. Knowledge of this association will favor early diagnosis and appropriate treatment.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Systemic Absorption of Topical Tacrolimus in Metastatic Crohn Disease With Skin Ulcers☆

Absorción sistémica de tacrolimus tópico en enfermedad de Crohn metastásica con úlceras cutáneas

To the Editor:

We present the case of a 54-year-old woman with colonic Crohn disease with metastatic Crohn lesions affecting the perianal region and skin folds. During an exacerbation she presented ulcerated intertrigo in the intergluteal, inguinal, and abdominal folds (measured surface area of ulceration of 155 cm^2, done with ImageJ software). After the administration of fentanyl and lorazepam for analgesia and anxiolysis, daily lavage was performed with soap and water and normal saline, and 60 g of topical 0.1% tacrolimus was applied using an impregnated swab. After 15 days, the nursing staff developed a new method for the daily application of the cream, emptying the contents of the tube into a pressure-lavage syringe and applying the preparation directly to the ulcers. Ten days later a moderate kidney failure was detected (elevation of creatinine from 1.4 mg/dL to 2.4 mg/dL and of urea from 69 mg/dL to 110 mg/dL). This was interpreted as prerenal failure and was treated by increasing fluid intake and intravenous fluids administration. However, suspecting the possible implication of tacrolimus in the deterioration of renal function, blood tests were performed and tacrolimus levels of 9.7 ng/mL were detected in whole blood (the therapeutic range after solid organ transplant is 5-20 ng/mL). The application of the cream was interrupted for 24 hours, and the level fell to 5.3 ng/mL. The concentration of the topical tacrolimus formulation was then reduced to 0.03%. Subsequent controls showed almost undetectable tacrolimus concentrations, and the serum creatinine fell to previous values.

Discussion

Cutaneous manifestations of CD occur in 9% to 23% of patients.[1] Perianal fissures and fistulas are probably the most common lesions (17%-43% of patients).[2] Metastatic CD is defined as the presence of compatible granulomatous lesions in skin that is not contiguous with the digestive tract.[3]

Topical tacrolimus administered once a day has shown a limited effect on the clinical course of fistulas and ulcers, achieving remission in 36% of patients and some response in 29%.[4] Regarding its side effects, Shah et al.[5]considered the most common to be mild pruritus at the site of application; they added that absorption through skin lacking the epidermal barrier or through the mucosas is usually low, giving rise to low or undetectable blood levels. Other authors have described elevated blood concentrations of tacrolimus after its application to the skin. Faisal[6] reported a level of 14.7 ng/mL associated with nausea, paresthesia, and dizziness, which he attributed to absorption through the gastrointestinal mucosa in a case of perianal CD. Russell et al.[7]described a patient with orofacial involvement in whom the application of 0.05% tacrolimus to an area of 1-2 cm^2 produced blood concentrations of 9 ng/mL and the patient developed thoracolumbar herpes zoster. Olson et al.[8] defined a series of risk factors for increased transcutaneous absorption of tacrolimus: the surface area involved, the absence of the skin barrier, and the use of occlusive dressings. Neuman et al.[9] added a further 2 factors: young age and warm skin due to increased circulation. They recommended monitoring tacrolimus blood levels in patients with 1 or more of these factors.

In our patient, the application of topical tacrolimus directly over the skin fold ulcers coincided temporaly matched with a deterioration in her renal function. Other causative factors may be implicated, but tacrolimus blood concentrations of 9.7 ng/mL could certainly have

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