LETTER TO THE EDITOR

GIANT SCROTAL ELEPHANTIASIS: AN IDIOPATHIC CASE

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Scrotal elephantiasis is very rare disease in industrialized countries, where it is mainly due to surgery, irradiation or malignancies. It can be defined as idiopathic only when the possible congenital, infectious and compressive causes are excluded. We report a case of massive scrotal lymphoedema in an adult Caucasian patient, in Italy. He presented an extremely voluminous scrotal mass measuring 50 x 47 x 13 cm (weight 18 kg), which extended below his knees, invalidating all his daily activities. The patient was hospitalized in order to undergo to surgical treatment. Although genetic causes were searched and the possible role of infectious agents and compressive factors was evaluated, no etiology was ascertained. Histopathologic examination showed non-specific chronic inflammation, confirming the diagnosis of idiopathic elephantiasis. One year after surgical treatment, the patient is healthy without recurrence signs.

Scrotal lymphoedema or elephantiasis is a rare and invalidating deforming disorder of the external genitalia, characterised by massive enlargement of the genitalia, which may be congenital or acquired (1). It is mostly secondary to filariasis or to *Chlamydia trachomatis* (lymphogranuloma venereum, LGV) infection (2-3) or due to vessel or lymphatic obstruction (4-5).

Congenital lymphoedema is divided into 3 groups depending on the age of the patient when it appears. Milroy's disease is a dominant autosomic disease associated with the *VEGFR-3* gene mutations in chromosome 5q; it presents in newborns or during infancy, however the onset may be much later, with less severe and localized involvement, as common in dominant disorders (6-7). Meige's disease or precocious lymphoedema presents in puberty, usually during adolescence, with a probable dominant autosomic disease of variable penetration (8). Late lymphoedema presents in adults over 35 years of age (9). Sometimes no apparent cause is found and the syndrome is classified as idiopathic scrotal elephantiasis (10-12). We report a case of massive scrotal lymphoedema in an adult Caucasian patient (aged 37 years).

Case report

In June 2008, a 37-year-old, heterosexual male, was admitted to the Plastic Surgery Department of the University of Rome "Campus Biomedico". He presented an extremely voluminous scrotal mass measuring 50 x 47 x 13 cm, which extended below his knees, invalidating all his daily activities. Clinical examination revealed an uneven papillomatous

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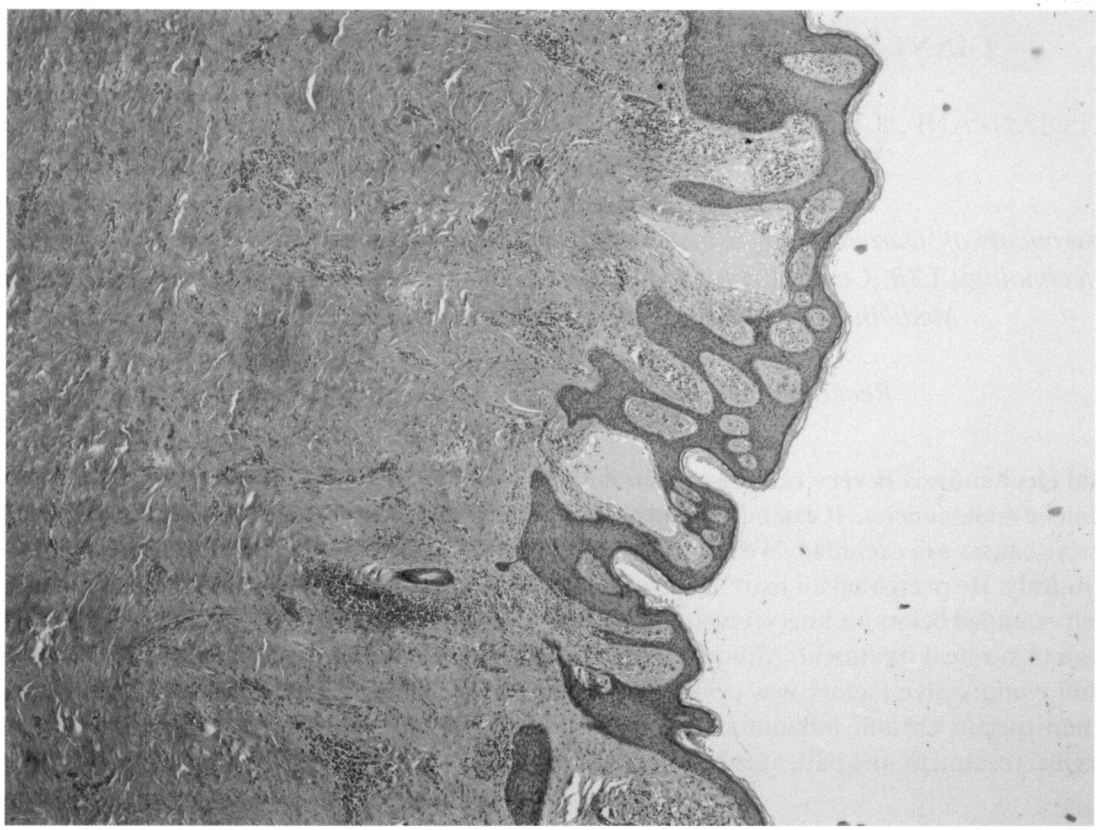

Fig. 1. *Ematossilin-eosin stained histological section (4x10 HPF) showing epidermal papillomatosis, dermal dense lymphoplasmacellular infiltrate, abundant fibrocollagenous mixedematous tissue and dilate lymphatic vessels.*

surface which covered the penis shaft, as well as the whole scrotum having a hard consistency. The urethral orifice was barely visible emerging from the huge mass, and the penis was no longer visible. No inguinal adenopathy was present. Most of the cutaneous surface was covered by irregular excrescences, with superficial bacterial super-infection which caused horrible odours and great discomfort for the patient. The cultures revealed the presence of *Enterococcus faecalis* and *Streptococci* and the patient was treated with specific antibiotic therapy.

The patient had noted the beginning of the disease 6 years previously, but referred a significant increase in scrotum dimensions in the previous two years. During anamnesis the patient declared to have had no sexual contacts in the previous 10 years, and no surgical procedures nor radiation therapy. Furthermore, he denied having ever left southern Italy to travel abroad; he lives in a farm house in the country, with poor hygienic conditions and close to domestic and farm animals.

The patient was affected by insulin-dependent diabetes mellitus type 2, hypertension and gout (all under pharmacological treatment).

Serological tests for late syphilis (*Treponema pallidum* particel agglutination test), chlamydiosis (Elisa anti-*Chlamydia trachomatis*, IgG), tuberculosis (tuberculin tine test) and brucellosis (Brucella micro-agglutination test) were negative. The patient was then hospitalized in order to undergo surgical treatment.

Laboratory evaluation, including blood count, metabolic panel, and sedimentation rate were within normal limits. Pre-operative and intra-operative microbiological cultures were negative for any kind of bacterial growth. MRI and CT identified the presence of bilateral external inguinal hernias not including bowel, distorted penile and testicular structures, excluding all the possible causes of compression to the lymphatic drainage.

Several biopsies were performed in order to

evaluate the histological alteration of the whole area. Histopathologic examination of the biopsies from the scrotal area revealed hyper- ortho-, para-keratosis and acanthosis of the epidermis, diffuse dermal inflammatory infiltrate mainly surrounding blood vessels and dilated lymphatic spaces. Periodic-acid Schiff and silver methenamine stains were negative.

Moreover, the papillomatous surface of the scrotal mass, the rapid growth and the infiltrative tendency led to suspect a possible viral role as the origin of the pathology; therefore biopsy samples were employed in a Human Papillomavirus (HPV) test. The DNA was extracted from the inner part of the excised tissue to exclude superficial contamination. Two different PCRs followed by sequencing (13-15) were performed to identify about 45 different genital HPV types; both tests gave negative results.

At the same time, from blood sample lymphocytes, cultures were performed in order to exclude genetic syndromes: the chromosome pattern showed no alteration. The DNA extracted from scrotal biopsies was employed to identify eventually present cellular mutations. In particular, the vascular endothelial growth factor receptor 3, *VEGFR3* gene (also known as *FLT4* gene) was screened by sequencing analysis. Mutations in the *VEGFR3* gene are known to cause Milroy disease (16). Each of the exons (exons 16-26) that encode the tyrosine kinase domains of VEGFR3 were amplified using the *Taq* DNA polymerase (Qiagen). The resulting PCR products were treated with QIAquick PCR Purification Kit (Qiagen) and then submitted to the PRIMM DNA Sequencing Core (http://www.milano.primm.it/client/dnaseq.asp) for sequence analysis. Primers were designed using GenBank accession number NM_182925 as the reference sequence and were synthesized by PRIMM (San Raffaele Biomedical Science Park, Italy). Analysis of the *VEGFR3* gene did not show any mutation in the considered regions.

It was decided to treat the incredibly invalidating condition with surgery: after a difficult isolation of the penis, spermatic cords and testicular structures, surgical excision of the scrotal mass (weight 18 kg) and subsequent circumcision were performed. A complex perineo-scrotal reconstruction was attempted in order to obtain coverage of the exposed structures and restore penile function. Testicles were covered with V-Y thigh septo-fascio-cutaneous advancement flaps. Penile shaft was covered with full thickness skin grafts.

Histopathologic examination did not reveal the presence of any microorganism or parasite, showing non-specific chronic inflammation and confirming the diagnosis of idiopathic elephantiasis (Fig.1).

DISCUSSION

Scrotal elephantiasis represents a medical challenge in terms of etiological diagnosis and surgical treatment. The disease is very rare in industrialized countries, where it is mainly due to surgery, irradiation or malignancies (17). It can be defined as idiopathic only when all the possible infectious, genetic and compressive causes are excluded. In the examined case, various factors could have contributed to the development of the neo-formed mass, such as previous misdiagnosed infections, poor hygienic and cultural conditions and other unknown environmental factors, but no etiological cause was found.

Surgical treatment is mandatory in those chronic organized forms, regardless of their diagnosis, in order to obtain a correct urination, deambulation and sexual function.

Moreover, no recurrence has been reported after a follow-up of six months to 10 years in male patients with non-STI-related genital lymphoedema treated with surgical reduction (1).

In this case, at the last clinical examination, one year after the surgical procedure, the patient was healthy, without signs of recurrence.

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