LICHEN SCLEROSUS AS A CAUSE OF RECURRENT CYSTITIS: CASE REPORT AND REVIEW OF THE LITERATURY

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[Lichen sclerosus come causa di cistiti ricorrenti: caso clinico e revisione della letteratura]

SUMMARY

Lichen sclerosus (LS), also known as '*lichen sclerosus et atrophicus*', is an acquired, chronic, inflammatory, fibrotic and atrophic disease, usually affecting skin, particularly genital region. It affects women, with a median age of 50 years. No etiological factor is actually known, nevertheless several risk factors have been proposed, including genetic predisposition, trauma, infections, and hormonal, metabolic and autoimmune diseases. Symptoms are deeply different: from mouth and/or anal/rectal dermatological manifestations, to urological disorders, whose most common are stranguria and dysuria. Here we described a case of a woman, affected by recurrent cystitis, stranguria and pelvic pain. Therefore, we reviewed etiological, clinical and histopathological aspects of this uncommon and difficult to identify disease, especially respect to its urinary complications.

Key words: lichen sclerosus, recurrent cystitis, vulvar squamous cell carcinoma.

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Introduction

Lichen sclerosus (LS), also known as 'lichen sclerosus et atrophicus', is a chronic inflammatory disease, affecting skin and mucosa, characterised by autoimmune tissues atrophy. Every region of the body can be affected, but both in men and women it particularly occurs in genital areas, i.e. anogenital region. The median age is about 50 years, although it may be observed at any age, and children may be affected too. The disease is more common in women than men. In women, LS is, by far, the most frequent vulvar dermatosis. The male form of LS has been referred to as balanitis xerotica obliterans, correlating with anatomic location, clinical appearance and histological findings of this condition. The disease has to be diagnosed, treated, and carefully followed-up, as there is a definite, though small, risk of squamous cell carcinoma development.

In this report, we describe the case of a 54-years-old woman, who presented with recurrent cystitis, straguria and dysuria, secondary to urinary outflow obstruction due to LS. Diagnosis was very difficult because of the extremely localized lesion[1-6].

Case report

A 54-years-old woman was admitted to our Department, in November 2010, for recurrent cystitis.

In 2005, she had been diagnosed with high blood pressure, and treated with ACE-inhibitors. In April 2010 she fractured her left wrist, and lesion was treated by plaster. Since August 2010 she suffered from recurrent cystitis (at least 4 episodes during the last 3 months), with straguria and dysuria, causing several admittances to citizen emergency rooms and taking levofloxacin, fos-

fomicin and others beta-lactam antibiotics, without any benefit. In October 2010 her urine culture was positive to Escherichia coli (1.000.000 CFU/ml), sensitive to cefotaxime, ceftazidime, cotrimoxazole and fosfomycin. In November 2010 she was admitted to the Department of Emergency Medicine of our University Hospital due to persistence of strangury and dysuria. She was discharged with diagnosis of 'abdominal pain in patient affected with recurrent cystitis and high blood pressure'. During hospitalization, she underwent gynecological and urological examination, both negative, and to abdominal basal computerized tomography (CT), with evidence of liver angioma.

The same month, after few days, she was readmitted to our Department of Emergency Medicine due to the persistence of the above mentioned symptoms, associated with pollakiuria, urinary urgency, sense of ipogastric and vaginal weight, and urethral meatus burning, without any other symptoms and/or signs implying others organs and systems. Then she underwent surgical (which suggested colonscopy) and gynaecological (negative) examination, and abdominal basal CT, that showed a colonic diverticular disease.

Therefore, she was transferred to our Department for further investigation and appropriate treatment. Nothing remarkable emerged from physical examination, except for onychomycosis of the fifth finger of the right foot, lower intensity of the left common carotid pulse, murmur 2/6 Levine heard over the mitral, aortic and tricuspid areas, pain in epigastrium and lower abdominal quadrants.

The haematochemical and instrumental investigations, performed during hospitalization, were not successful to define the exact nature and origin of symptoms/signs that aimed the admission. The patient underwent urological, gynaecological (completed with transvaginal ultrasound), gastroenterological examinations, together with lower basal abdomen CT (positive detection of Bence-Jones protein in urine), cystography, cystoscopy, sigmoidoscopy ('diverticulosis of the sigmoid colon'), with substantially negative results.

Finally, a further gynecological examination, afterward confirmed by a dermatological visit, diagnosed the presence of a periurethral LS, with partial obliteration of urethral meatus, which explained the reported symptoms and the recent history of recurrent cystitis, due to urinary outflow obstruction. Then the patient was treated with antibiotics (cotrimoxazole plus metronidazole, both i.v. and orally), associated with topical steroid treatment. Therefore, the patient improved and was discharged with indication to periodical gynaecological and dermatological follow-up to evaluate effects of therapy and evolution of disease.

Discussion

LS is an acquired, chronic, inflammatory, fibrotic and atrophic mucocutaneous disease, of unknown aetiology. The median age is about 50 years, although it may be observed at any age, and children may be affected too. It mainly occurs in women, but its true epidemiology is, yet, not well known, because affected patients may have no symptoms, and those with symptoms may be too frightened or embarrassed to seek help. However, some studies demonstrated a female to male ratio of 10:1, others of 1:1, depending from examined population and diagnostic criteria[7,8].

No clear etiological factor has been identified, and there are conflicting evidences about genetic factors (familial LS and association with class II HLA DQ7, DQ8, DQ9 and interleukin 1 receptor antagonist (IL-1ra) gene expression, which may be associated with extension and severity of lesions)[9-11] traumas (extragenital LS has been reported at clothing fractioning sites and presence of Koebner phenomenon may be founded at sites of lesion, so trauma, injury and sexual abuse have been suggested as possible triggers)[12,13], infections (Borrelia burgdorferi genome has been isolated from lesions)[14], sex hormones metabolism abnormalities (a reduction of dihydrotestosterone levels has been demonstrated)[15], autoimmunity disorders (association with vitiligo, alopecia areata, autoimmune thyroid disease and systemic lupus erythematosus; moreover, IgG autoantibodies against extracellular matrix protein 1 (ECM-1) have been detected in 67% of patients, even if they are not presumed to be pathogenic)[16,17], together with connective tissue alteration (increased elastase activity, loss of dermal elastic tissue, increased glycosaminoglycan secretion and absence of collagenasis)[18], and immunocytological alterations (peripheral and lesional reduction of CD3 [all T cells] and CD4 [T helper cells] count, evidence of T cell lesional activation, raise of CD1a+ Langerhans cells in all histological phases of LS, increased IL-6 immunoreactivity and p53 expression enhancement)[19-24].

The disease primarily affects the anogenital mucocutaneous area. In women, a characteristic

vulvar, perineal and perianal pattern has been likened to an eight or a keyhole, and may extend to the medial surface of thigh. Contrariwise, men present mainly involvement of the glans penis, whereas anal localization is almost rare. Most of affected women manifested vulvar intractable itching, soreness and pain. Dysuria, dyspareunia, apareunia, frigidity, reduced frequency of sexual intercourses, anal itching, and pain on defecation are other common symptoms, but often the patients are completely asymptomatic.

Some patients have persistent, following treatment, vulvar dysesthesia, indicating an associated vulvodynia. This could be the basis of apparent treatment failure cases. In males, first presenting symptom of this disease can be easily phimosis. Both in females and males, extragenital involvement is often asymptomatic, whereas, sometimes, severe pruritus can be associated. It may occur in 2-15% of affected and range from a single papule to a widespread outbreak, although the latter is unusual. The most common sites are neck, shoulders, wrist and sub mammary area. Rarely it may be affected scalp, oral cavity, palms and soles too.

Generally, genital lesions features are pallor, hyperkeratosis and atrophy (mainly affecting labia minora and inner labia majora); sometimes telangiectasia, purpura, erosions, tender fissures in the labial sulci and perianal area and, rarely, haemorrhagic blisters may occurs too. Extragenital lesions appear as pale macule or papule, which may coalesce into plaques, and rarely itch. LS may also cause anatomical changes, i.e. fusion of labia minora, leading to obliteration of interlabial sulci, and adhesion of mucosa overlying clitoris and urethral opening, which can lead to phimosis and obstruction of urinary outflow[25-30].

Morphology of LS is usually characteristic and a clinical diagnosis can be made in most women via examination of anogenital mucocutaneous area. Diagnosis must be histologically confirmed, without biopsy from eroded skin if possible. As a matter of fact, histologic features are more specific than clinical ones. Optical microscopy usually shows variable epithelial thinning, with 'loss of network ridging', and, sometimes, massive overlying keratosis can be detected. Hydropic degeneration of the basal layer is often the most striking features, but typical features of histological framework are edema and homogenization of collagen in overlying dermis, associated with elastic fibres reduction and monocytic, lymphocytic and mast cells infiltration. This inflammatory infiltrate seems to reflect LS clinical course, which is a chronic relapsing remitting one[31,32].

It's also important considering possibility of coexistence of Candida and bacterial infection in patients with LS undertaking appropriate microscopically and cultural investigations, if clinically indicated[33].

Risk of malignant transformation may be due to scratching-connected epithelial hyperplasia. Some, recent studies noticed possibility of LS evolution to squamous cell carcinoma in 4-5% of affected women. The real extent of neoplastic transformation in diagnosed and treated LS in not known, nevertheless it is considered appropriate to carry out a long-term follow-up. Furthermore, immunocytochemical studies show aberrant p53 expression in lesion, as well as, by PCR, it is possible to isolate the genome of human papilloma virus[34,35].

Differential diagnosis between LS and lichen planus (LP) is usually simple, both clinically and histologically, although it can be difficult on mucosa sites. Evidence pointed out existence of LS/LP overlap syndrome and it has been hypothesized these conditions may represent transitional stages of a unique disease, rather than coexistence of both[36].

According to age and site of presentation, several specialists, as paediatricians, gynaecologists, urologists, dermatologists, and internal medicine physicians can manage LS. As in our case, this leads to diagnostic difficulty and fragmented approach, due to lacunose knowledge of the disease.

No curative therapy is actually known, and only symptomatic treatments can be used. Bland emollients, such as emulsifying ointment or aqueous cream, are safe and generally well tolerated. Patient should be informed of necessity keeping good anogenital hygiene, and should be advised to wear cotton clothes and avoid little comfortable and occlusive clothing. Corticosteroid ointments, applied twice daily for 2-3 months, can provide effective relief of symptoms in most patients, and can be considered treatment milestones of anogenital LS. Furthermore, systemic steroid therapy can be used for extensive mucocutaneous disease. In addition to steroid, antibiotic therapy may be given, both local and systemic, alone or in combination, if a bacterial infection coexists, i.e. metronidazole.

Old therapies, based on local use of androgen and/or progestin creams, have, nowadays, no more

useful evidence. As late, therapy with retinoid and immunosuppressive drugs (cyclosporine and calcineurin inhibitors) can be considered: first showed excessive cutaneous irritation, the other having no relevant percutaneous adsorption. There are no more indications for surgery, except for surgical separation of mucosa adhesions (phimosis or urine flow obstruction), and vulvectomy if there are unequivocal evidences of neoplastic progression. Moreover, healed patients should be warned of possible LS resurgence, and advised to contact again the physician at recurrence of symptoms and/or lesions. Aforesaid reinforces, even more, the need of long-term follow-up[37-42].

In conclusion, considering our patient, we can explain its recurrent cystitis as induced by anatomical reduction of urinary outflow. Difficulties in diagnosis were due to lack of typical symptoms/signs of LS and physicians unfamiliarity with the disease. As a matter of fact, if men usually present phimosis, women easily might be totally asymptomatic. So, LS should be considered in differential diagnosis of recurrent cystitis, resistant to antibiotic therapy, especially if young women without any known associated risk factor (immunosuppression, diabetes, cystocele, uterine prolapse, urinary or reproductive tract surgery, and risky sexual behaviour) are the affected patients. Furthermore, sequenced follow-up should be considered, both to verify effectiveness of topical or systemic therapy, to evaluate occasionally recurrence of the disease and to exclude possible, even if extremely rare, evolution to squamous cell carcinoma.

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