Condyloma acuminatum in childhood-systemic lupus erythematosus patients

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ABSTRACT

Introduction: Infections are frequent in childhood-systemic lupus erythematosus (C-SLE) patients, including human papillomavirus (HPV). HPV infection may cause genital and anal warts named condyloma acuminatum (CA). To our knowledge, none case was reported and the prevalence of CA in C-SLE population was not performed.

Case Reports: From January 1983 to May 2012, 5,682 patients were followed at the Pediatric Rheumatology Unit from of our University Hospital and 289 (5%) of them met the American College of Rheumatology classification criteria for C- SLE. Four (1.4%) of our female patients had CA. The median age at diagnosis was 13 years. Three of them were sexually active and all of them had active disease and had high risk HPV anogenital warts. Pap smears showed low-grade squamous intraepithelial lesion, guided biopsies identified chronic cervicitis, vulvar, vaginal, anal and/or cervix intraepithelial neoplasia. All of them were under corticosteroids and immunosuppressive drugs. The visible genital warts lesions were eradicated.

Discussion: Our patients requires rigorous gynecologic follow-up due to the severe anogenital dysplasia. HPV vaccine should be indicated in all C-SLE prior to sexual activity.

Keywords: Adolescent; Childhood; Systemic Lupus Erythematosus; Human Papillomavirus; Infection; Condyloma acuminatum.

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INTRODUCTION

Infections are an important cause of morbidity and mortality in our childhood-systemic lupus erythematosus (C-SLE) patients,[1] including genital infections, such as human papillomavirus (HPV)[2].

Adult patients with SLE, particularly those on immunosuppressive therapy, have cervical dysplasia with detection of HPV infection varying from 4.7 to 50%[3-10]. In C-SLE, we previously reported suggestive lesions of HPV infection in 2% of these patients[2].

In addition, this genital abnormality is induced by the proliferation of squamous epithelial cells secondary to this virus infection and was rarely described in adult SLE[11]. To our knowledge, none case was reported and the prevalence of condyloma acuminatum in children and adolescents C-SLE patients was not performed.

Therefore, from January 1983 to May 2012, 5,682 patients were followed at the Pediatric Rheumatology Unit from Instituto da Criança da Faculdade de Medicina da Universidade de São Paulo and 289 (5%) of them met the American College of Rheumatology (ACR)[12] classification criteria for SLE. Four (1.4%) of our female C-SLE patients had condyloma acuminatum with confirmation of HPV DNA testing by Hybrid Capture 2 (HC2 high-risk; Digene Corporation, currently QIAGEN, Gaithersburg, MD, USA), using DNA of oncogenic group (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 e 68). None of our male C-SLE patients had condyloma acuminatum.

Pap smears were evaluated by the same cytopathologist blinded to gynecology examination in our University Hospital. They were performed according to the 2001 Bethesda Classification System[13] in 5 patterns. Guided biopsies were performed on all identifiable lesions at colposcopy.

This study was approved by the Local Ethics Committee of our University Hospital. Demographic data, clinical and laboratory findings, disease activity[14] and

damage[15] scores, treatment regimens and outcome of our four female C-SLE patients at IA diagnosis are shown in Table I, and their cases were reported herein.

CASE REPORT

CASE 1

A 12 year-old female was admitted to our University

TABLE I. DEMOGRAPHIC DATA, CLINICAL AND LABORATORY FINDINGS, PAP SMEARS, DISEASE ACTIVITY/DAMAGE, TREATMENTS AND OUTCOME IN CHILDHOOD-SYSTEMIC LUPUS ERYTHEMATOSUS (C-SLE) PATIENTS AT *CONDYLOMATA ACUMINATUM* (CA) DIAGNOSIS

	Cases			
Variables	**1**	**2**	**3**	**4**
Demographic data				
Age at JSLE diagnosis, years	12	8	14	15
Period between JSLE and CA, months	22	108	1	48
Age at menarche, years	10	11	10	12
Age at first sexual intercourse, years	14	16	-	16
Clinical features at CA	Vulvar warts	Vulvar, vaginal, and anal warts	Vulvar and anal warts	Vulvar warts
Pap Smears at CA	LSIL/ASCH	LSIL	-	LSIL
Histological findings	CC, metaplasia	CIN 3, VIN 2, AIN 1	Papilomatosis	CC
Laboratory findings at CA				
Haemoglobin, g/dL	11.2	11.8	12.2	10.8
Leukocytes/mm^3	5,600	5,800	5,500	9,100
Lymphocytes/mm^3	1,792	1,102	440	600
Platelets count/mm^3	276,000	254,000	140,000	338,000
Urinalysis				
Leukocytes/mL	670,000	16,000	140,000	11,000
Erythrocytes/mL	1,800	19,000	3,000	79,000
Urea, mg/dL	20	33	33	25
Creatinine, mg/dL	0.2	0.9	0.96	1.0
Proteinuria, g/24h	0.35	0.8	0.23	0.8
CRP, mg/dL	9.85	2.41	6.6	0.62
ESR, mm/1sth	42	27	26	48
Disease activity and damage at CA				
SLEDAI-2K	6	14	20	19
SLICC-ACR/DI	0	0	NA	0
HPV isolation	HPV DNA of oncogenic group and cervix biopsy	HPV DNA of oncogenic group, cervix biopsy, HPV 16	HPV DNA of oncogenic group, HPV 16	HPV DNA of oncogenic group
Treatments at CA				
JSLE therapy	CT, AZA, AM	CT, AZA, AM	CT, IVCYC, AM	CT, AM
HPV	LEEP	CO2-laser vaporization	Surgical removal	LEEP
Recurrence of HPV/CA	Yes	–	–	–

ASCH = Atypical squamous cells of undetermined significance that cannot exclude high-grade squamous intraepithelial lesion, LSIL = Low-grade squamous intraepithelial lesions, CC = chronic cervicitis, CIN = cervical intraepithelial neoplasia, VIN = vulvar intraepithelial neoplasia, AIN 1 = anal intraepithelial neoplasia, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, CT = corticosteroid, AZA = azathioprine, AM = antimalarials, IVCYC = intravenous cyclophosphamide, LEEP = loop electrosurgical excisional procedure, SLEDAI-2K - Systemic Lupus Erythematosus Disease Activity Index 2000, SLICC/ACR-DI - Systemic Lupus International Collaborating Clinics/ACR - Damage Index, NA – not applicable.

Hospital with malaise, fever, malar rash, and arthritis in ankles and knees. Her laboratory exams identified hemoglobin 8.4g/L, white blood cell count (WBC) 5.000/mm³ (56% neutrophils, 38% lymphocytes, 1% eosinophils and monocytes 5%), platelets 262,000/ /mm³ and negative Coombs test. Immunological tests showed antinuclear antibodies ANA 1:320 (fine speckled pattern), and positive anti-double-stranded DNA (anti-dsDNA), anti-Sm, anti-RNP and IgG anticardiolipin antibodies (14.0 GPL). C3 was 0.33 mg/dL (normal 0.5-1.8), C4 0.051mg/dL (normal 0.1-0.4), urea 25 mg/dL (normal 10-42), creatinine 0.5 mg/dL (normal 0.6-0.9), C-reactive protein (CRP) 3.2 mg/L (normal < 5) and erythrocyte sedimentation rate (ESR) 56 mm/1st hour. The proteinuria was 0.6 g/24h and urinalysis showed granular casts, hematuria 208,000/ml, leukocyturia 162,000/ml, and the diagnosis of C-SLE was confirmed according to the ACR criteria. The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score was 27, and she was treated with chloroquine 5mg/kg/day and prednisone 60mg/day. The menarche was 10 years and at 13 years and 10 months, her menstrual cycles were irregular. The age onset of sexual activity was 14 years, with three sexual partners. At that moment, the gynecologic clinical examination of the genitalia showed vulvar warts suggesting condyloma acuminatum. *Chlamydia trachomatis* was also identified by Hybrid Capture 2 (HC2 CT-ID; Digene Corporation, currently QIAGEN, Gaithersburg, MD, USA). The following serologic tests were negative: hepatitis virus A, hepatitis virus B, hepatitis virus C, Epstein-Barr virus (EBV), cytomegalovirus (CMV), human T-lymphotropic virus (HTLV) and human immunodeficiency virus (HIV). The Pap smear showed LSIL according the 2001 Bethesda System[13]. Laboratory findings, SLEDAI-2K and Systemic Lupus International Collaborating Clinics/ACR-Damage Index (SLICC/ACR-DI) were 6 and 0, respectively (Table I). She was under prednisone 20mg/day, azathioprine 150mg/day and chloroquine 250mg/day. External genital warts were treated with loop electrosurgery and all visible lesions were eradicated. At 16 years old, she had new vulvar warts, Pap smears showed ASCH and Digene HPV test by HC2 showed DNA of oncogenic group. At that moment, colposcopically guided biopsies demonstrated chronic cervicitis with metaplasia and HPV identification. External genital warts were treated with loop electrosurgery and genital warts in the cervix with loop electrosurgical excisional procedure (LEEP). All visible lesions were eradicated.

CASE 2

The 8-year-old female was admitted to the pediatric unit of our university hospital with fever, arthralgia (knees, ankles and wrist), malar rash, oral ulcers, pleuritis, pericarditis and arterial hypertension. Her laboratory exams identified hemoglobin 8.4 g/dL, hematocrit 26%, leucocytes 25,000/mm³ (61% neutrophils 36% lymphocytes, 1% eosinophils and monocytes 2%), platelets 70,000/mm³, creatinine 1.2 mg/dL, urea 89 mg/dL, C3 42 mg/dL (normal 79-152) and C4 3.3 mg/dL (normal 15-38). The proteinuria was 0.15 g/24h and abnormal urinalysis (155,000 erythrocytes/mL and 302,000 leukocytes/mL). Immunological tests showed ANA 1/200 (homogeneous pattern) and positive anti--dsDNA, and negative anti-Ro, anti-La, anti-Sm and anticardiolipin antibodies. ESR was 66 mm/1st hour and renal biopsy showed diffuse proliferative nephritis (class IV of World Health Organization). The diagnosis of C-SLE was confirmed according to the ACR criteria and the SLEDAI-2K score was 21. She was treated with prednisone (2mg/kg/day) with progressive dose decrease, chloroquine 250mg/day and intravenous cyclophosphamide (500-1000 mg/m²) for three consecutive years. The age at menarche was 11 years with regular menstrual cycles after 13 years. At 17-years--old, the gynecologic clinical examination of the genitalia showed diffuse warts on vagina, vulva and perineal regions suggesting condyloma acuminatum. *Chlamydia trachomatis* was not isolated by HC2 CT-ID and following serologic tests were negative: hepatitis virus A, hepatitis virus B, hepatitis virus C, EBV, CMV, and HIV. At that moment, she was under prednisone 20 mg/day, chloroquine 250mg/day and azathioprine 150mg/day, and her laboratory findings, SLEDAI-2K 14 and SLICC/ACR-DI 0 are shown in Table I. Pap smears showed LSIL and Digene HPV test by HC2 showed DNA of oncogenic group. The age onset of sexual activity was 16 years and only one sexual partner. Colposcopically guided biopsies were performed in three locations and demonstrated: condyloma with koilocytosis, eosinophilic border and nuclear atypia (Figure 1), CIN 3 in the cervix (Figure 2), vulvar intraepithelial neoplasia (VIN 2) and anal intraepithelial neoplasia (AIN 1). HPV-16 was identified in vulva and endocervix by immunohistoquimic assay. She was treated with CO2-laser vaporization in the genitalia without eradication of all visible lesions and LEEP in the cervix.

CASE 3

A 14-year-old female was admitted in our University

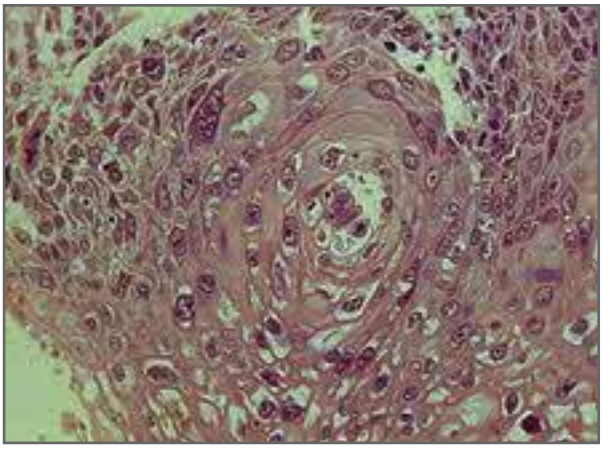

FIGURE 1. Condyloma with koilocytosis, eosinophilic border and nuclear atypia

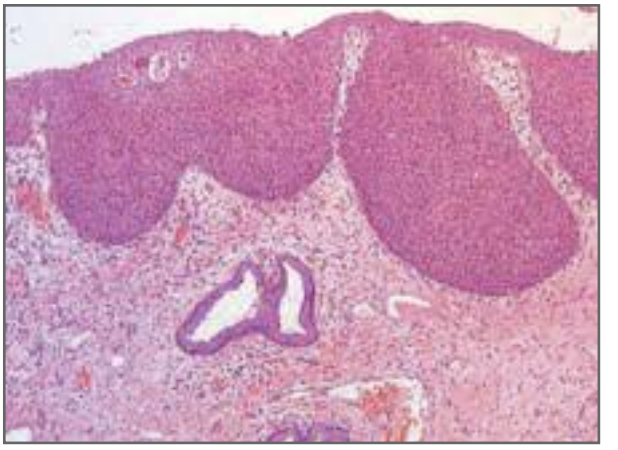

FIGURE 2. Cervical intraepithelial neoplasia (CIN 3) in the cervix

Hospital with fever, malar rash, petechiae, psychosis and severe alveolar hemorrhage. Her examinations identified hemoglobin 9.1 g/dL, hematocrit 26.9%, WBC 4,930/mm³ (78% neutrophils 16% lymphocytes, 1% eosinophils and 5% monocytes), platelets 37,000/mm³, urea 22 mg/dL and creatinine 0.74 mg/dL. Immunological tests showed ANA 1/1280 (homogeneous pattern), positive rheumatoid factor and anti-dsDNA, and negative anti-Sm, anti-RNP, anti-Ro, anti-La and IgG and IgM anticardiolipin antibodies. C3 was 26 mg/dL (normal 79-152), C4 2 mg/dL (normal 15-38), ESR 62 mm/1st hour and CRP 15.8 mg/L. Urinalysis showed 1000 leukocytes/mL and 1000 erythrocytes/mL, and proteinuria was 1.023 g/24h. The diagnosis of C-SLE was confirmed according to the ACR criteria and the SLEDAI-2K score was 20. She was hospitalized in the intensive care unit and received methylprednisolone 1 g/day for three days, intravenous cyclophosphamide (750 mg/m²), hydroxychloroquine 300mg/day and prednisone (2.0 mg/kg/day) with improvement of psychosis and alveolar hemorrhage. After one month of hospitalization, the gynecologic clinical examination of the genitalia showed vulvar and anal warts suggesting condyloma acuminatum with intact hymen. The following serologic tests were negative: hepatitis virus A, hepatitis virus B, hepatitis virus C, CMV and HIV. At that moment, her menstrual cycles were irregular and the age at menarche was 10 years. No history of sexual intercourse and sexual abuse was reported. Laboratory findings, SLEDAI-2K and SLICC/ACR-DI are shown in Table I. Perineum and anal biopsies demonstrated papilomatosis, with identification of HPV-16 by chromogenic in situ hybridization. The Digene HPV test by HC2 showed DNA of oncogenic group in vaginal ostium undertaken by *Cytobrush* ®. She was treated with warts surgical removal procedure in the perineum and anus with total improvement.

CASE 4

An 8-year-old female was admitted in our University Hospital with chronic idiopathic thrombocytopenic purpura with petechiae and bruising on the lower limbs. She had autoimmunity family history of SLE (her brother, maternal aunt and maternal grandmother) and Sjögren syndrome (her mother). Her examinations identified hemoglobin 10.2 g/dL, hematocrit 32.3%, WBC 6,300mm³ (48% neutrophils, 41% lymphocytes, 6% eosinophils and 5% monocytes) and platelets 15,000/mm³. Immunological tests showed ANA 1:200 (speckled pattern) and positive lupus anticoagulant, and negative anti-dsDNA, anti-Ro and anti-La antibodies, and rheumatoid factor. C3 was 91 mg/dL (normal 79-152), C4 9 mg/dL (normal 15-38) and ESR 37mm/1st hour. She was treated with prednisone (2.0 mg/kg/day) with gradual dose reduction. At 15 years old, she had malar rash, arthritis in knees, upper limbs vasculitis, arterial hypertension and her examinations showed proteinuria was 0.6 g/24h and urinalysis showed granular casts, hematuria 15,000/ml, leukocyturia 31,000/ml. The diagnosis of C-SLE was confirmed according to the ACR criteria and the SLEDAI-2K score was 24. She was treated with prednisone (1.0 mg/kg/da) and chloroquine (250mg/day). At 19 years, the gynecologic clinical examination of the genitalia showed vulvar warts suggesting condyloma

acuminatum. The following serologic tests were negative: hepatitis virus B, hepatitis virus C, CMV, *Chlamydia trachomatis* and HIV. Her menstrual cycles were regular after menarche at 12 years. The age onset of sexual activity was 16 years and only one sexual partner. Laboratory findings, SLEDAI-2K 19 and SLICC/ /ACR-DI 0 are shown in Table I. She reported condom in all sexual intercourses without hormonal contraceptive use. At 19 years, she received prednisone 5 mg/day and chloroquine 250mg/day, the Pap smears showed LSIL and Digene HPV test by HC2 showed DNA of oncogenic group and colposcopically guided biopsies demonstrated chronic cervicitis. She was treated with LEEP with total improvement.

DISCUSSION

This was the first report that evaluated the prevalence of condyloma acuminatum in a large population of C--SLE patients from a university pediatric hospital, and clearly showed that this infection occurred in female sexually active and virgin patients with disease activity and under immunosuppressive agents.

Of note, female C-SLE patients are becoming adolescents and became sexually active with a consequent higher risk of sexually transmitted disease (STD), such HPV.[2] HPV is known as the most common STD in United States females and the major risk factor is younger age at coitarche (first sexual intercourse)[16], as observed in three of our C-SLE patients.

In addition, the incidence of anogenital warts was approximately 1% in sexually active adults and may be up to 3% in sexually active adolescents[17]. The most frequently types associated with these lesions are HPV 6 and 11, contrasting with our four cases and other reports[18] that presented the oncogenic group with a marked risk to dysplasia and cervical cancer.

On the other hand, condyloma acuminatum was also observed in our lupus patients without coitarche and sexual abuse history. Indeed, HPV infection may be related to autoinoculation or heteroinoculation, through direct contact or fomites in these patients, as described in one of our cases. A recent study reported anogenital HPV infections in girls before sexual activity, diagnosed by the same routine Hybrid Capture II HPV DNA test, as used in the present cases[18].

Interestingly, *Chlamydia trachomatis* is the most common bacterial cause of STD and the prevalence of this endocervical infection was 3% in a recent adult SLE Brazilian study[5]. The same study did not observe a higher frequency of HPV associated with this genital infection[5]. *Chlamydia trachomatis* infection was observed in one of our sexually active lupus patient, and to our knowledge this genital infection was not reported in juvenile systemic lupus erythematosus population.

The most important risk factors associated to general infections in C-SLE population are related to disease itself (activity[1,2] and lymphopenia) and treatments (corticosteroids and immunosuppressive drugs)[1,10]. Of note, in adult SLE immunosuppressant, especially azathioprine and cyclophosphamide use, was the main risk factor for HPV infection[3,4,6-11].

The treatment of condyloma acuminatum includes physical destruction in the anogenital area, such as surgical removal with loop electrosurgical excisional and CO2-laser vaporization,[17] as indicated in our cases.

Therefore, we would recommend routinely gynecologic evaluation and HPV infection testing before start immunosuppressive drugs in adolescent SLE patients. Importantly, HPV vaccine should be indicated in all C--SLE patients, particularly before start sexual intercourse. Recently, the quadrivalent HPV vaccine was safe and effective in adult lupus patients older than 18 years and did not induce disease activity or flares[19]. Immunogenicity and safety of this immunization should be also known in the C-SLE population.

In conclusion, condyloma acuminatum was rarely observed in C-SLE population, mainly after coitarche and in virgin patients with disease activity and/or under immunosuppressive agents. Our patients requires rigorous gynecologic follow-up due to the severe anogenital dysplasia.

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