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Systemic Lupus Erythematosus Onset in a Young Woman with Human Papilloma Virus Infection

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Abbreviations: SLE: Systemic Lupus Erythematosus; HPV: Human Papilloma Virus; DNA: Deoxyribonucleic Acid; RNA: Ribonucleic Acid; EBV: Epstein Barr Virus; ANA: Antinuclear Antibodies; anti-dsDNA: Anti-Double Stranded DNA Antibodies; CRP: C - Reactive Protein; ESR: Erythrocyte Sedimentation Rate; LN: Lupus Nephritis; GC: Glucocorticoids; MMF: Mycophenolate Mofetil; HIV: Human Immunodeficiency Virus; VLPs: Purified Virus-Like Particles.

Abstract

Nowadays the exact pathophysiological processes underlying Systemic Lupus Erythematosus (SLE) development remain unknown. Factors, which seem to contribute to disease onset is a strong genetic predisposition but also an environmental influence. Among environmental factors, viral infection may play an important role, leading to immune system dysfunction in several ways. Human Papilloma Virus (HPV) is a non-enveloped double stranded DNA virus and is the best known sexually transmitted infection in men and the immune system cross reactivity with its proteins may have a role in SLE pathogenesis.

This report describes a case of a woman who was admitted to our rheumatology ward because of widespread edema and progressive dyspnea of recent onset and because of the presence, in her medical history, of signs of a possible systemic autoimmune disease. A diagnosis of Lupus Nephritis was made according to the 2012 Systemic Lupus International Collaborating Clinic criteria and in the meantime, the patient received a diagnosis of invasive squamous cell cervical cancer secondary to HPV infection after the histologic report of conisation she underwent three weeks previously. SLE patients are at increased risk for infection, owing to the dysregulation of their immune system as well as the immunosuppressive therapy, in particular SLE patients have a higher prevalence of HPV than the general population, independent of number of sexual partners or immunosuppression.

Another point to reflect is the link between malignancy and SLE: Many mechanisms have been hypothesized that seem to play a role for different types of cancer such as immunosuppressive therapy, SLE activity, viral agents and genetics.

In light of this, it is important to underline the role of preventive HPV vaccination in SLE patients and it is essential that the safety, immunogenicity and efficacy of this vaccine in this specific population be studied.

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Introduction

Up to now the exact pathophysiological processes underlying Systemic Lupus Erythematosus (SLE) development remain unknown, although several mechanisms have been proposed [1].

Of course, there is a complex interaction between genetic and environmental co-factors leading to disease onset. A strong genetic predisposition has long been proposed, as disease concordance rate is approximately 25% in monozygotic twins, but only 2% in dizygotic twins. However, there is also a strong environmental influence [2]. Among environmental factors viral infection may play an important role, leading to immune system dysfunction in several ways such as molecular mimicry, altered apoptosis of the host cells, exposure of as yet masked antigens to the immune system by a given microorganism, and direct viral invasion of immunocompetent cells [3].

Some genetically determined deficit of the immune system may contribute, such as complement factors deficiency, deficit of mannose binding lectine, causing insufficient clearance of infectious agents, whose persistence in the host may determine autoimmunity, and the production of autoantibodies by infected B-lymphocytes leading to the expression of particular microRNA in these cells [4]. Viruses may also promote the development of autoimmunity by their association with components of the RNA interfering pathway [3].

Among all infectious agents, Epstein Barr Virus (EBV) is the one most frequently claimed to be associated with SLE, but also Human Papilloma Virus (HPV) has been supposed to promote the disease [5].

HPV is a non-enveloped double stranded DNA virus with a tropism for basal mucosal and cutaneous epithelia and is the best-known sexually transmitted infection in men. The molecular structure of HPV has many aspects in common with human proteins, such as lupus ku autoantigen, autoantigens proteins p86 and p70, lupus brain 1 antigen homolog, lupus antigens expressed in neurons and muscles, natural killer cell IgG like receptor, complement proteins C4A and C4B, complement receptor CD19, and the immune system cross reactivity with these proteins may have a role in SLE pathogenesis [6]. Herein it is presented a case of a women with a recent lupus nephritis onset and a concomitant diagnosis of invasive cervical squamous cell carcinoma.

Case report

A 43 year-old caucasian women was admitted to the emergency room of our hospital because of widespread edema and progressive dyspnea of recent onset. In addition, she reported a history of Raynaud's phenomenon, and arthritis of the hands, wrists and feet since two years. Because these symptoms, she was transferred to our rheumatology ward, with the diagnosis of possible systemic autoimmune disease. She had a history of HPV 16 infection, and three weeks previously had underwent a procedure of conisation for high-grade squamous intraepithelial lesion. Upon examination the patient was afebrile with widespread edema, and blood pressure was slightly elevated. Serum blood tests revealed the presence of antinuclear antibodies (ANA, titre 1:160, homogeneous pattern by indirect immunofluorescence on HEp2 cells), anti-double stranded DNA antibodies (anti-dsDNA, by IFI on Crithidia lciliae), low C3, low C4, proteinuria (1104 mg in 24 hour), decreased glomerular filtration rate (34,73 ml/min), anemia (hemoglobin 10 mg/dL), raised C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR). Computed chest tomography and echocardiogram were normal, while abdominal ultrasound scan showed fluid in the pelvic region.

In addition, a percutaneous renal biopsy was performed. Histology showed diffuse proliferation with mesangial expansion, increased cellularity and capillary thickening. There were no crescents, necrosis or thrombi. These findings were suggestive of class IV *Lupus Nephritis* (LN) with elements of class V, according to the International Society of Nephrology/Renal Pathology Society 2003 classification system [7]. The patient received a diagnosis of SLE according to the 2012 Systemic Lupus International Collaborating Clinic criteria [8]. She was started with high-dose oral Glucocorticoids (GC), ACE inhibitors and a prophylactic dose of enoxaparin, with marked clinical improvement after few days. In the meantime, the histologic report of the conisation came to our attention, showing invasive squamous cell carcinoma. The patient was transferred to gynecology ward and she underwent complete hysterectomy with concomitant local lymphadenectomy without complications. Following the recovery from the surgical procedure, Mycophenolate Mofetil (MMF) 2 gr/day was added to tapering GC for SLE treatment.

After one month her renal function and 24-hour proteinuria improved (to 51,85 ml/min and 740 mg/24 hr, respectively), arthritis disappeared, hemoglobin level, ESR, CRP, C3, C4 returned to normal range, anti-dsDNA became negative. After six months the patient was asymptomatic, proteinuria disappeared and had normal renal function, while on MMF 2 gr/day and prednisone 5 mg/day.

Discussion

This case report describes SLE onset, with SLE nephropathy, in a young woman with HPV infection and invasive squamous cell carcinoma of the cervix, requiring hysterectomy. There is a complex interplay between SLE and microbes, with evidence that both viral and bacterial infections may be involved in the development of SLE and trigger flares in established cases [9,10]. The molecular structure of HPV has similarities with some human lupus autoantigens, and crossreactivity may well be a mechanism leading to SLE in a genetically predisposed individual [11]. Moreover, SLE patients are at increased risk for infection, owing to the dysregulation of their immune system as well as the immunosuppressive therapy [12], and it is well documented that SLE patients have a higher prevalence of HPV than the general population, independent of number of sexual partners or immunosuppression [13].

It has been supposed that SLE patients are more prone to develop cervical dysplasia/cancer and vulvar/vaginal cancer, as they are both associated with HPV infection and patients with SLE are more susceptible to HPV infection due to decreased viral clearance. There have been many studies examining the risk of malignancy in adult patients with SLE. These studies are based either on observational clinical cohorts or cohorts identified through administrative data such as hospital discharge and national health insurance databases.

Several individual cohort studies have reported that the risk of hematologic and nonhematologic malignancies such as lung, liver, head and neck, thyroid, vaginal/vulvar, cervical (cancerous and precancerous), skin, bladder or renal, anal, and pancreatic are increased in SLE patients [14]. Many potential risk factors have been hypothesized linking malignancy and SLE, such as

immunosuppressive therapy, SLE activity, viral agents, genetics, playing distinct roles for the different type of cancer. Virus-induced carcinogenesis can be enhanced by additional factors such as tobacco smoking and co-infection with other sexually transmitted infections such as Human Immunodeficiency Virus (HIV), Chlamydia trachomatis, Herpes Simplex virus type 2, or with multiple HPV types [15,16]. Among HPV positive women, the use of oral contraceptive for 5 years or more and parity (5 or more pregnancies) was associated with an increased risk of cervical cancer. The prevention of HPV infection is of great importance for decreasing the incidence of cervical cancer in SLE population. The 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases recommends patients, particularly those with SLE, should receive HPV vaccinations [17]. Annual cervical cancer screening is recommended in 2018 Canadian Rheumatology Association (CRA) guidelines [18]. From 2009, two prophylactic HPV L1 Virus-Like Particle vaccines namely, Gardasil®; quadrivalent (Merck) and Cervarix™-bivalent (GlaxoSmithKline) are widely commercially available.

Since 2011, the Costa Rica Vaccine Trial (CVT) and PATRICIA trials have provided evidence that a single dose of the bivalent HPV vaccine provides strong durable protection against HPV16 and 18, and suggest additional benefit of cross-protection against phylogenetically-related HPV types [19].

Gardasil is a quadrivalent Human Papilloma Virus (HPV4) vaccine that was approved for use by the US Food and Drug Administration in June 2006. HPV4 vaccine is routinely recommended for administration to women in the USA who are 11-12 years old, quadrivalent Human Papilloma Virus (HPV4) vaccine is prepared from the purified Virus-Like Particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18 [20]. Another issue is if these vaccines may be responsible for autoimmune disease onset. Autoimmune manifestations compatible with SLE or SLE-like disease have been described in six women who presented with lupus symptoms following HPV vaccination [21]. Anyway, a clear linkage between these events has never been demonstrated.

Doubts about vaccine safety have been one of the principal obstacles for the acceptance of HPV vaccination by the public. It is therefore of primary importance to provide the public with clear and up-to-date information about HPV vaccination safety. SLE patients should benefit from preventive vaccination, therefore, it is essential that the safety, immunogenicity and efficacy of the HPV vaccine in this specific population be studied [22].

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