

Unraveling a systemic lupus erythematosus diagnosis

Abstract

Kim (A patient's pseudonym) a black female was 22 years old when she first entered the Rehab Center. She was diagnosed with Lupus although she did not have any obvious familial linkages to this disease. During the admission process to the facility, we discovered that Kim's stepmother who was not genetically related to her also had Lupus. Kim had grown up with her stepmother. Yet, we discovered that Kim's older stepsister did not have Lupus. This intrigued us. What could have caused her to get Systemic Lupus Erythematosus (SLE), a heterogeneous rheumatoid type disease caused by genetic and environmental influences, and which affects African Americans and other minorities more severely than whites from European descendants? Kim also had End-Stage Renal Disease (ESRD) and was on dialysis three times a week.

Keywords: systemic lupus erythematosus, environmental factors, genetic markers

Volume 9 Issue 3 - 2019

Suzette A Henry, David Newton, Stashauna Kelly, Tony L Brown

Major General Hugh G. Robinson Center, USA

Correspondence: Tony L Brown, Major General Hugh G. Robinson Center, USA, Email tbrown@post.harvard.edu

Received: May 31, 2019 | **Published:** June 17, 2019

Abbreviations: SLE, Systemic Lupus Erythematosus; ESRD, End-Stage Renal Disease; LN, Lupus Nephritis; Dnmt, DNA methyltransferase; RA, Rheumatoid Arthritis; ACPA, Anti-Citrullinated Protein/peptide Antibodies; IC, Immune Complex; GBM, Glomerular Base Membrane; MCP, Monocytes Chemoattractant Protein

Introduction

The purpose of this article is to affirm the literature and show that Kim's SLE was caused by combined factors of genetic and environmental agents. Kim already had a genetic predisposition for SLE. Yet, although her immune system was susceptible to SLE, Kim's exposure to environmental factors in the Bronx, New York, could have triggered genetic changes within her gene and chromosomes. After two years of being admitted to our Rehab Center, Kim had a double hip replacement, a stool transplant due to frequent and chronic C-diff infection; she also mourned her stepmother's death due to Lupus. Kim's condition raised two questions: How did she get Lupus? And what is the phenotype and genotype of this disease? Recently, Kim suffered a relapse related to her diagnosis of Lupus. After spending two weeks post admission, she was discharged from the hospital. She complained that she didn't receive physical therapy during her recent hospital experience and she felt overwhelmed with feelings of general weakness, especially to her lower extremities.

Case presentation

Systemic Lupus Erythematosus (SLE) is a genetic disease/phenotype that is caused by various mutations on the chromosome. Common signs of SLE include malar rash, photosensitivity, kidney disease, arthritis, anemia, low platelet and white blood cell.¹ Incidences of SLE equal 1-10 per 100,000 persons per year, with prevalence 20-70% per 100,000.² One of the major complications of SLE is Lupus Nephritis (LN). LN patients will have damage in their proximal convoluted tubule of kidney and 25% will develop End Stage Renal damage within ten years after their diagnosis of LN. SLE with its remissions and flare-ups affect some ethnic groups more readily than others and females more than male. Research show that Hispanics, Asians, Native American and Afro-Americans have a higher "incidence, prevalence, morbidity, and mortality, than whites of European decedents".³

The prevalence of SLE has increased in the last 40 years. This has resulted in the highest rate of motility of all the rheumatoid disease classification.⁴ LN also has a higher prevalence among these ethnic groups. The overall prevalence and incidence of SLE ranges from 1.4% to 21.9% and from 7.4 to 159.4 cases per 100,000 people respectively.³ These statistics are very alarming for the minority community and females.

More ominous, minorities living in a lower socioeconomic group are at a higher risk of getting SLE. The reasons for this are partly due to environmental forces and healthcare restraints within their communities. Based on our own experience, other contributing factors that make minorities more susceptible to Lupus are: environmental toxins, misdiagnosis, and lack of medical follow-ups and more regular physicians' visits. Yet, there are multiple genetic and environmental influences that could have caused Kim SLE disease and complication of LN.

Environmental factors

A review of the literature generally indicates that environmental triggers can influence patients who already have a genetic predisposition toward having SLE. What are those environmental triggers? They include but are not limited to cigarette smoke, chemicals Hg, Silicia, UV lights, viral infections, and medications.⁵ These environmental triggers affect patients' DNA in many segments including: DNA methylation, histone changes that take place in cytosine base of the DNA, deacetylation, the ubiquitin to the substrate protein of DNA, and trimethylation of histone tails of DNA.⁵ These processes are needed in the cell to stop unwanted and dangerous genes from replicating and functioning.

During mitosis, the enzymes - DNA methyltransferase (Dnmt) catalyzes the DNA methylation process. However, when environmental triggers interfere with Dnmt, the trigger stops the "off" or "silence" that is supposed to occur in DNA methylation mitosis process, and causes hypo methylation of the DNA especially in the CD4 T-cells. This in turn causes the T cells of SLE patients to be auto reactive to MHC11 molecules, without increasing the signals from auto antigens.⁵ Put differently, the body's antigens fight against itself.

However, it is the regulation of Dnmt and the lack of the methyl group during mitosis that cause some of the T cells subset to be atypical in the CD4, TH1 and TH2 cells. This interference in the DNA demethylation process produces “oxidative stress” which decreases protein Kinase C phosphorylation and which decreases extracellular signal- regulated kinase (ERK). This process is responsible for regulating the Dnmt levels. In fact, ERK have been found to be suppressed in SLE patient’s CD4 T –cell count.⁵ In other words, environmental triggers cause the cell to display immune responses against its own antigen resulting in regulation and decrease Dnmt. This leads to hypo methylation of DNA in CD4 T cells, further causing the inflammatory process (proinflammatory cytokines) SLE. Knowing how these environmental triggers work could help us unravel Kim’s diagnosis of Lupus.

What in Kim’s environment would have caused her to develop SLE? Kim recently moved to Georgia from Bronx, New York. However, she was diagnosed with Lupus before relocating. Growing up in the inner city of the Bronx New York, she was exposed to many environmental toxins that could have awakened her Lupus disease. Smoking is one of the risk factors associated with Rheumatoid Arthritis (RA). A history of smoking or exposure to smoking could influence whether or not you develop RA. Kim could not remember whether or not she was exposed to second- hand smoke in the Bronx, and denied that her step- mother had ever smoked. We believed that even if no one in Kim’s immediate family smoked, she was exposed to smoking. Bronx, NY is one of the poorest boroughs in the USA, with asthma cases being higher than the national average.⁶

Although we do not know why the asthma average in the Bronx is so high, there are certain conditions that can cause the risk of asthma morbidity. These include household environmental exposure and tobacco smoke.⁶ The same smoke that increased the number of asthma could have also caused genetic changes in the SLE patient and by the same token could have caused Kim’s Lupus. Exposure to smoking is linked to 1.3 to 2.4 times increased risk of RA onset. This relationship between smoking and RA is strongest among people who are ACPA-positive (anti-citrullinated protein/peptide antibodies), a marker of autoimmune activity.⁶ Still, aside from environmental influences, we also should consider other factors.

Genetic markers

What genetic markers can cause SLE? There are many gene and chromosomes that could have cause Kim’s SLE. The gene and chromosome that affect Afro-American include:

Gene	Chromosome
HLA	6p21
IRF5	7q32
STAT4	2q32
TNFAIP3	6q23
ITGAM	16p11
FCGR2A	1q21-23

In a patient with SLE, the effect occurs in all levels of their immunity including their innate immunity.³ Kim might have been born with the gene for SLE and lived in an environment that predisposes her to getting the disease. Having these pre- disposing factors prompted her development of the disease. But we still need to understand how these genetic markers work.

SLE patients have errors within CD4, TH1 and TH2. The cell started to leak DNA and RNA genetic components into the extracellular membrane. The genetic material is picked up by dendritic cells. The dendritic cells present the antigen to the T cells, and the T cells activate the B cells; the B cells release antibodies that target DNA. The joining of the antibody and DNA or protein material create an immune complex (IC). The IC includes antinucleosomes, anti-double-strand DNA, DNA extractable nuclear antigen antibodies, and antibodies against sections of the complement system (CLq that clean out IC). This IC is first deposited in the glomerular base membrane (GBM) , mesangium, and in the proximal tubule epithelial cells of the Kidney. The Dendritic receptors, which are there to identify foreign materials in the body, recognized and bind the IC and to the nucleosome (histones and DNA), which in turn signal the release of proinflammatory cytokines and chemokines such as monocytes chemo attractant protein 1 (MCP-1), interleukin 1, and 6 (IL-1 and IL-6) and adhesion molecules. Together these strings of interactions create a chronic inflammatory process.³

The effects of all this inflammatory process do not occur in a vacuum. The overwork of the innate immunity becomes a target for monocytes influx, and infiltration, which causes endothelial cell injury. This leads to release of type 1 interferon and development and penetration of T cells. This ongoing process causes the increase in T helper 2 lymphocytes (TH2), the T helper cells 1 (TH1), and T helper cells 17 (TH17).³

Furthermore, the UV light triggered apoptosis and protein, which created IC complex. Exposure to virus such as Epstein Barr binding with antigen can create IC.³ Both the environment and genetic factors led us to conclude that Kim already had a gene for Lupus. However, her disease was triggered by some environmental factors. These factors caused apoptotic debris not to be completely clean away, thus creating IC complexes that led to the amplification of Kim’s T cells. Both the inherited traits and environmental triggers produced a chronic inflammatory response that is SLE.⁷

Discussion

This study found that though Kim had a genetic predisposition to SLE; the effect of the disease was finally induced by environmental agents. Exposures to environmental factors in the Bronx, New York, most likely explain the evidence of genetic transformation in her gene and chromosomes. Reviews of the literature on environmental and genetic agents were accurate in their agreement about the importance of these factors combined operating in a deadly manner to trigger lupus. . Indeed, with the lack of educational material often available for families who live in underserved communities, imply that nurse practitioners, family doctors and other healthcare workers should alert families with disposition to SLE, of the adverse effects that certain environmental factors could have on the children diagnosed with SLE. Early educational interventions may be one of the most cost-effective means of suppressing or managing SLE patients, and could lead to improved quality of life and longer life spans, especially for African Americans. Notwithstanding this observation, underscoring the value of the environment on SLE is radically different from economically depressed families having the resources, to effectively mitigate environmental dynamics. Furthermore, additional research could focus on how well early educational interventions in community clinics, churches (since most African Americans are associated with faith-based communities), and inner-city schools could influence

where genetically predisposed SLE families may choose to reside. In underserved minority communities where visual pedagogies and face-to-face instructions are more effective than educational reading materials, healthcare providers need to be well versed in innovative strategies that could reduce the triggering of SLE.

Acknowledgments

We would like to show our gratitude to two anonymous reviewers for sharing their wisdom during the course of this research. Although they may not agree with all of our interpretations or conclusions, all errors are our own and should not tarnish the helpful insights of these esteemed reviewers.

Conflicts of interest

There were no financial gain or personal considerations or unbalancing of institutional mission that compromised or had the appearance of compromising the researchers' judgement in conducting this research.

References

1. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of Systemic Lupus Erythematosus. *Arthritis Rheum.* 1997;40(9):1729.
2. Pons-Estel GJ. Understanding the epidemiology and progression of Systemic Lupus Erythematosus. *Semin Arthritis Rheum.* 2010;39(4):257–268.
3. Salgado AdZ, Daiz HC. Lupus Nephritis. An overview of recent findings. *Hindawi Publishing Corporation Autoimmune Disease*, 2011; 1–2.
4. Williams EM, Ortiz K, Browne T. Social Determinants of Health, the Chronic Care Model, and Systemic Lupus Erythematosus. *Int J Chronic Dis.* 2014;361792.
5. Mak A, Tay SH. Environmental Factors, Toxicants and Systemic Lupus Erythematosus. *Int J Mol Sci.* 2014;15(9):16043–16056.
6. Warman K, Silver EJ, Wood PR. Modifiable Risk Factors for Asthma Morbidity in the Bronx vs. other Inner-City Children. *J Asthma*, 2009;46(10):995–1000.
7. <http://www.cdc.gov/arthritis/basics/rheumatoid.htm>.