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Malignant Melanoma Association with Systemic Lupus Erythematosus in a Large Midwestern U.S. Patient Population-A Retrospective Study

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Systemic Lupus Erythematosus (SLE), an autoimmune disorder with chronic inflammation, may enhance cellular dysplasia leading to uncontrolled tumor cell proliferation.^{1,2} The mechanism for tumorigenesis in patients with SLE has not been delineated, but although an increased risk for Non-Hodgkin's and Hodgkin's lymphoma, and for laryngeal, lung, liver, vaginal, vulvar, thyroid, and non-melanoma skin cancers (NMSC) have all been reported,^{1,3–5} an association with malignant melanoma (MM) remains unclear. The highest incidence of MM for males and females, as recently reported, is in Caucasians (29.7 males and 19.1 females per 100,000) and lowest in Asian males and African American females (1.1 males and 1.0 females per 100,000).⁶ Given the reported relatively low incidence of MM and the relatively high incidence of SLE in African American females^{7,8}, the specific aim of this study was to determine if an association exists between SLE and a subsequent diagnosis for MM within a large, urban, Midwestern U. S. patient population.

The Northwestern Medicine Enterprise Data Warehouse (NMEDW), (>4 million patients), an urban, medical record data repository, was searched for data (January 2001 – December 2016) from both dermatology and rheumatology patients, aged 18–89 years, who had a diagnosis of SLE (ICD 9 or 10 codes: 710.0, M32.1–M32.14, M32.8 and M32.9), and, as a control to minimize potential selection bias, we also extracted data from patients who had a diagnosis of systemic sclerosis (SS; ICD 9 or 10 codes: 710.1, M34.0, M34.1, M34.8, M34.9). From these, data from patients with a diagnosis of MM (ICD-9 or 10 codes: 172.0–172.9 and C43.0–C43.9) at least 6 months after SLE or SS diagnosis were extracted for analysis. Fisher's exact test was utilized to assess for an association.

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Data for a total of 4,027 patients with a diagnosis for either SLE (N=2351) or SS (N=1676) were evaluable for analysis. The characteristics of these patients are shown in Table 1. Of the 2,351 patients diagnosed with SLE, 11 had a subsequent diagnosis of MM, a statistically significant association ($p=0.03$). The association remained significant after adjusting for age ($p=0.04$). The median time between SLE diagnosis and MM was 96 months (IQR 16–136.5 months).

Cao, et al., performed a meta-analysis of five U.S. and European studies published between 1997 and 2013⁴ and using the general population as a control, found a decreased risk for MM in patients with SLE (Pooled RR = 0.65 (95% CI, 0.50–0.85) Egger's test $p=0.952$).⁴ Of note, although Dreyer, et al. found an association for NMSC with SLE compared to the general population (SIR 2.0 [95% CI, 1.2–3.6]), there was a non-significant, but trend to positive, association for MM with SLE (SIR 1.3 (95% CI, 0.3–5.2)).⁹

Study limitations include collection of data from a single center, urban, patient population that may not be representative of the general population. Additionally, the resulting small MM sample size did not allow for further analyses.

Considering that the evolving management of malignant disorders (such as MM of the skin) with checkpoint inhibitors (anti-CTLA-4 and anti-PD-1) carries the potential to aggressively disrupt immune reactivity and to trigger uncontrolled cellular responses in patients such as those with SLE^{1,2}, further exploration of the association between malignant melanoma and SLE is warranted in order to promote optimal patient management. Moreover, the findings from this study highlight the importance of follow-up with routine surveillance for melanoma in patients with SLE.

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Characteristics of SLE and SS populations with and without a subsequent diagnosis for malignant melanoma of the skin.

Table 1

	SLE patients (N=2351)		SS patients (control) (N=1676)		Total
	MM	No MM	MM	No MM	
Overall	10 (0.04%)	2341 (99.96%)	1 (0.06%)	1675 (99.94%)	4027
Sex:					
Male	1 of 256 (0.4%)	255 (99.6%)	0 (0%)	280 (100%)	536
Female	9 of 2095 (0.4%)	2086 (99.6%)	1 of 1396 (0.01)	1395 (99.99%)	3491
Race:					
White	7 of 922 (0.8%)	915 (99.2%)	1 of 869 (0.01%)	868 (99.9%)	1791
Black or AA *	2 of 575 (0.3%)	573 (99.7%)	0 (0%)	158 (100%)	733
Asian	1 of 90 (1.1%)	89 (98.9%)	0 (0%)	32 (100%)	122
Other	0 (0%)	268 (100%)	0 (0%)	161 (100%)	429
N/A	0 (0%)	413 (100%)	0 (0%)	364 (100%)	777
Missing	-	-	-	-	175

* AA = African American

N/A = Not available (not documented)