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Military Toxin Exposure and Multiple Myeloma: A Cohort Study Through Natural Lan-Guage Processing Queries

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Abstract

Multiple myeloma is a cytogenetically heterogeneous clonal plasma cell neoplasm and almost always preceded by an asymptomatic premalignant stage termed Monoclonal Gammopathy of Undetermined Significance (MGUS). It has been recognized that numerous environmental factors and genetic events appear to trigger the progression of multiple myeloma. This is a cohort-based study that uses combination of structured clinical information from Montefiore medical records and Natural Language Processing (NLP) of all clinical notes associated with the patients. We investigated multiple myeloma and its potential association with military services, and tox-in exposures (such as agent orange, pesticides) in patients admitted to Montefiore Medical Center during the past five years. Our study showed a statistically significance ($p<0.0001$) in developing MM in patients with histories of military service and toxin exposure compared to the control group. The NLP query showed very low percentage of military service records in the patients with MM diagnosis in Montefiore medical records. Further study should set up standard criteria of military service by using Bronx Regional Health Information Organization (RHIO) base evidence. For the Veterans who had potential toxin exposures, perhaps it would be a good idea to consider routine clinic visits and screening testing such as serum electrophoresis and immunofixation for early detection of MGUS and MM.

Keywords: Myeloma; Health information organization; Immunoglobulin

Introduction

Multiple myeloma is a bone marrow–based, multifocal plasma cell neoplasm associated with an M-protein in the serum and / or urine. The disease spans a clinical spectrum from asymptomatic to aggressive forms and disorders due to deposition of abnormal immunoglobulin chains in tissues. The diagnosis is based on a combination of pathologic, radiologic, and clinical features.

Events mediating progression from the pre-malignant Monoclonal Gammopathy of Undetermined Significance (MGUS) to Multiple Myeloma (MM) are unclear. Several genetic abnormalities that occur in tumour plasma cells play major roles in the pathogenesis of myeloma. Primary early chromosomal translocations occur at the immunoglobulin switch region on chromosome 14(q32.33). Secondary late-onset translocation and gene mutations that are implicated in disease progression include MYC activation, TP53 and FGR3 mutations among other genetic abnormalities [1].

Numerous environmental factors and genetic events appear to trigger the progression of multiple myeloma. Previously cohort and case control studies have reported an elevated risk of multiple myeloma among agricultural workers, and Vietnam Veterans with agent orange exposure. A prospective cohort study by Dr. Landgren included 479 Vietnam Veterans with exposure of agent orange and 479 comparison Veterans [2]. The study discovered that Vietnam Veterans have a significantly increased risk of MGUS, supporting an association between agent orange exposure and multiple myeloma. Multiple myeloma has been classified as exhibiting "limited or suggestive evidence" of an association with exposure to herbicides in Vietnam Veterans.

Materials and Methods

We first identified a cohort of 2329 patients diagnosed with MM. The inclusion in this cohort was ascertained by at least one occurrence of MM diagnosis including MM in remission, plasma cell leukaemia in remission, or plasma cell leukaemia in relapse in a cohort of 736,707 adult patients (age>21 years old) with an inpatient, outpatient, Telehealth, or home visit between January 2016 to January 2023 in Montefiore Medical Center, Bronx, New York. All clinical notes associated with both

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Table 1: Multiple Myeloma Cohorts Group Compared to Study Populations in the Database.

	Base Cohorts	Military Service	Toxin Exposure	Military/Toxin Exposure
Study Populations (denominator)	736707 (100%)	19734 (3%)	1976 (0.3%)	69 (0.01%)
Multiple myeloma	2329 (0.3% of 100%)	16 (0.1% of 3%)	8 0.4% of 0.3%)	6 (9% of 0.01%)

Table 2: Myeloma Patients with Demographic Information and Toxin Exposures.

Myeloma patients	Age/sex/race	Military Services	Toxin Exposures	Visit setting
Patient 1	89/ male/ Hispanic	yes	37569	oncology
Patient 2	62/ male/ Hispanic	no	pesticides	oncology
Patient 3	73/ male/ unknown	yes	agent orange	oncology
Patient 4	71/ male/ Hispanic	yes	Vietnam veteran	primary care
Patient 5	71/ male/ White	yes	agent orange, 911 WTC	oncology
Patient 6	89/ male/ Hispanic	no	pesticides	urology
Patient 7	80/ male/ unknown	yes	no	primary care
Patient 8	73/ male/ African American	yes	no	oncology
Patient 9	55/ male/ White	yes	pesticides	primary care
Patient 10	84/ male/ African American	yes	no	primary care
Patient 11	82/ male/ White	yes	no	oncology
Patient 12	91/ male/ White	yes	no	primary care
Patient 13	90/ male/ African American	yes	no	pulmonary
Patient 14	74/ male/ African American	yes	no	primary care
Patient 15	85/ male/ African American	yes	no	primary care
Patient 16	76/ male/ African American	yes	no	oncology
Patient 17	81/ male/ Hispanic	yes	no	cardiology
Patient 18	71/ male/African American	yes	no	oncology

cohorts were processed using a custom NLP query to show cohorts of patients with military background (such as military service, Veteran, Vietnam war, Army, Navy, or air force). Another custom NLP query was used to identify cohort of patients with recorded history of toxic exposure (e.g., 9/11 world trade center, agent orange, mustard gas, sarin gas, pesticides, herbicides, fungicides). All queries and NLP results were reviewed by the authors to ensure extraction of relevant patients, encounters, and notes. The correlation between military / toxin exposures and MM was examined by chi-square test.

Results and Discussion

In our study, we identified 2329 patients with Multiple Myeloma (MM) diagnosis in a base cohort of 736,707 patients between January 2016 to January 2023 at Montefiore Medical Center, in Bronx, New York. The NLP query recognized a cohort of 69 patients with military service record and toxin exposure. In this group, six patients had diagnosis of MM (8.7%). A control group of 715,066 patients were identified, which have neither military records nor toxin expo-sure. In the control group, 2311 patients had diagnosis of MM (0.32%). There was statistically significant ($p<0.0001$) in developing MM in patients with military and toxin exposure com-pared to the control group (Table 1).

Of the 2329 myeloma cases in a base cohort of 736,707 patients, 16 cases (0.08%) had a history of military service, and 2313 cases (0.32%) did not have records of military services. This in-formation implies that military service itself did not appear to be a contributory factor in developing myeloma. However, we could not exclude the possibility such as lack of documentation or history intake during patient visits. Further study should set up standard criteria of military service by using Bronx Regional Health Information Organization (RHIO) base evidence. This would allow us to assess how well the NLP could detect histories of military services in Montefiore medical records. Table 2 showed the demographic characteristics of the myeloma patients with military service / or toxin exposure. Of the 18 patients, all are male patients, 39% were African American, and 22% were Caucasian. The records were predominately obtained during patient visits in primary care and oncology services. In the myeloma group with records of military services (Table 2), six patients had toxin exposure, and ten patients did not have exposure of toxin. Overall African American appears to have a higher incidence of MM diagnosis.

This finding concurred with the prior reports that myeloma is more common in African American compared with persons of European ancestry.

Previous studies reported myeloma has been inked to exposure to environmental agents such as agent orange, burn pits, and radiation [3]. The epidemiologic evidence on toxin and risk of MM is complex [4]. A more detailed examination of this relationship is necessary for informed risk assessment and public health awareness. Our analysis showed statistically significant between military history with toxin exposure and risk of MM. Small patient numbers are among the limitation of this analysis. Extended work needs to include a larger scale of veterans, and investigate toxin exposure in the Veteran population and its potential association with MM. Veterans who reported histories of agent orange and other toxin exposures may perhaps represent a group of patients with increased risk of MGUS and MM. Early screening testing (such as serum electrophoresis

and immunofixation) in this patient group could be used for early detection of MGUS and MM.

Finally, it would be important to study the survival of Veterans with MM diagnosis and toxin exposure. Unfavourable indicators for MM include high risk t (4;14) and the MAF translocations t (14;16) and t (14;20), and deletion of 17p/TP53 sequences. Further work should examine the survival data and its potential association with cytogenetic findings such as unfavourable prognostic indicators.

Our study demonstrated disproportionately high occurrence of MM in patients with recorded military services and toxin exposures when compared to the control group (p value<0.0001). This finding suggests some evidence of an association between military / potential toxin expo-sures and MM. Future study should set up RHIO base evidence of Bronx Veteran records as standard criteria, and further investigate the association between toxin exposure in the Veteran population and risk of MM.

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