37. LATE HEMATOLOGIC COMPLICATIONS OF MUSTARD GAS

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INTRODUCTION

Chemical warfare agents in general and mustard gas in particular were used by Iraq against Iranian combatants during the Iraq - Iran war from 1981 to 1988. Mustard affects many organs such as the skin, eyes, and lungs, as well as the gastrointestinal, endocrine, and hematopoietic system (1-6). Although some of these complications are transient or treatable in the early phases, late complications may remain for years. Alkylating effects of mustard gas disturb the DNA of hematopoietic cells (7-8). High-dose exposure has a cytotoxic effect on hematopoietic stem cells and pancytopenia has been seen in Iranian combatants (9). Low-dose effects on this system may appear years later and follow-up studies are needed to determine these adverse effects. One study showed initial marked lymphopenia in 36% of exposed patients while during the recovery phase, lymphocyte counts increased to greater than 40% in 18% of patients (10).Increase in lymphocyte protease activity in human peripheral blood due to mustard exposure has been reported(11). In another study, some neutrophil function tests remained intact despite mustard poisoning (12). There are thousands of handicapped patients who suffer from adverse effects of chemical warfare poisoning in Iran. We undertook this hematological survey to determine and assess the late complications of mustard gas poisoning.

MATERIALS AND METHODS

A case - control model study was undertaken from November 1998 to March 1999.
Patients: The case group was selected from chemical warfare victims of the Iran - Iraq war whose acute lesions had been diagnosed clinically at the field hospital based on known signs and symptoms of blistering agents. The case group had been under sulfur mustard (Lewisite) gas attacks, and revealing kits verified the gas in the field at the time of attack. All patients had certificates confirming their injury, issued by a medical commission.

Sampling was done randomly from 318 patients within 2300 male chemical warfare victims of the Isfahan province of Iran registered at the Center for Military Patients at the Amir Al-Momenin Hospital. Fifty-seven patients had had previous hematologic exams check - ups 3.2 years before our main examinations.

Controls: In order to disclude the effects of age and geographics, 700 male controls were selected from Isfahanian men referring to the Isfahan Thalassemia Prevention and Research Center for routine premarriage check-ups and thalassemia carrier screening. None had experienced contact with any chemical warfare agents.

Blood Tests: Blood samples of both groups were taken from venous blood, heparinized after sampling and tested within two hours. Just after sampling, two blood smears were prepared. The smears were studied after Gimsa staining, by an expert hematopathologist. CBC (RBC, WBC, MCV, MCH, MCHC, Hb, HCT) were done for all samples, using an automatic electronic cell counter (H*1,Technicon, France).

Statistical Analysis: Data was entered and analyzed (SYSTAT Win 5 software) using tests for means difference (two slope t- student test). P value less than 0.05 was considered significant. To evaluate qualitative variables relationships, chi- square test was used, and if

sparse cells (less than 5 in each cell) were observed, Fisher's exact test was preferred. Data was written in mean and standard deviation form. Decrease and increase in blood indices, beyond limits of the normal range , were evaluated compared to hematologic reference values of American males .

RESULTS

Blood indices of case group and controls are illustrated in table 1. Previous exam results of 57 chemical warfare victims are shown in a separate column in the table2.

RBC indices: Apart from MCV ($p<0.001$) no red cell index differed significantly between case and control groups. Macrocytosis was significantly higher in our main exams than the patient's previous exams (odds ratio = 15.8/0). Mean MCV and hemoglobin values were higher than previous examinations ($p<0.001$).

WBC indices: Apart from eosinophil count ($p=0.54$) other WBC related indices were found significantly higher in control group. Neutropenic condition (Odds ratio = 2.6) showed no difference in comparison with previous exams of the patients. Lymphocyte, monocyte, and eosinophil count were higher in the second examination.

Peripheral blood smear: Abnormal smears, observed in 42 cases, varied from hypochromasia in RBCs to 6.3 percent atypical lymphocyte visualization. In six patients atypical lymphocytes comprised more than 20 percent of the lymphocyte population and in the other patients atypia was less than 20 percent.

DISCUSSION AND CONCLUSION

Lungs, skin, eyes and bone marrow are the organs most involved in mustard gas poisoning. In some Iranian combatants pancytopenia has been an early complication of heavy mustard poisoning due to bone marrow involvement (10). The affected individuals presented highly over - rate B cells in parallel with the lowest percent of T cells in peripheral blood one week after exposure to mustard. After one year the B cell number fell to the highest of normal range while T cell number never reached even the lowest of the normal range (13). Studies on murine lymphocytes after in vivo treatment with mustard showed that B-lymphocytes were relatively more affected than T- lymphocytes (14). In our study although no evidence was found to show lymphocytosis or lymphopenia in our patients, decreased lymphocyte count in comparison to their previous results and the appearance of atypical lymphocytes suggest a lymphoid production disorder. Mustard alkylating effects cause reduction of stem cells to a critically low level. It may be due to DNA defects subsequent to mustard gas exposure (15). A decrease in count and dysfunction of pluripotent stem cells may occur after mustard poisoning and involvement of myeloid, lymphoid and erythroid cells in this study may be correlated with disarrangement in pluripotent stem cells. Neutropenia, decrease in neutrophil count and other leukocyte components, may also result by this mechanism. Stem cell failure can decrease marrow transit time of erythroid clones, and then elevation of erythroid concentration can increase erythrocyte mean corpuscular volume (16) and causes the production of large "stress" erythrocytes. Further studies on bone marrow cells and cell markers and long-term follow-up of patients are required to assess definite hematologic complications of mustard gas exposure.

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KEYWORDS
Hematologic, complications, mustard Gas, Iran, Chemical warfare

FIGURES AND TABLES

Table 1: Mean Value Of Hematologic Indices Between Case & Control Groups

Index	Control	Case	P.Value
Red blood cells (count)	5/66±0/82	5/64±0/51	0/35
Hemoglobin (gr/dl)	17/02±2/77	17/02±1/19	0/95
MCV (fentoliter)	90/38±8/25	86/67±5/46	<0/001
MCH	30/41±5/66	29/86±2/26	0/44
WBC (count/ml*1000)	6/70±1/31	6/98±1/16	0/03
Neutrophil (count/ml*1000)	3/60±1/31	4/09±1/39	<0/001
Lymphocyte (count/ml*1000)	2/26±0/62	2/09±0/62	0/001
Monocyte (count/mL*1000)	0/41±0/16	0/45±0/14	0/001
Eosinophil (count/ml*1000)	0/22±0/18	0/22±0/21	0/57

Table 2: Hematologic indices in case group

Index	First exam	Secound exam	P.Value
Red blood cells (count)	5/34±47%	5/52±%38	0/008
Hemoglobin (gr/dl)	15/52±1/06	16/91±0/98	<0/001
MCV (fentoliter)	84/45±6/51	91/76±5/9	<0/001
MCH	30/32±7/28	30/41±1/38	0/929
WBC (count/ml*1000)	7/36±2/34	6/72±1/73	0/059
Neutrophil (count/ml*1000)	4/46±2/33	3/68 ±1/73	<0/062
Lymphocyte (count/ml*1000)	2/51±0/64	2/17±0/68	0/001
Monocyte (count/ml*1000)	0/24±0/13	0/39±0/14	<0/001
Eosinophil (count/ml*1000)	0/24±0/16	0/2±0/13	0/047