Multiple Myeloma in World Trade Center Responders: A Case Series

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Objectives: *We report on cases of multiple myeloma (MM) observed in World Trade Center (WTC) responders registered in the WTC Medical Program.* ***Methods:*** *Possible cases of MM diagnosed between September 11, 2001, and September 10, 2007, in responders were confirmed if they met the World Health Organization and Mayo Clinic diagnostic criteria.* ***Results:*** *Among 28,252 responders of known sex and age, eight cases of MM were observed (6.8 expected). Four of these cases were observed in responders younger than 45 years at the time of diagnosis (1.2 expected). A slight deficit of MM cases was observed in responders older than 45 years (4 observed, 5.6 expected).* ***Conclusion:*** *In this case series, we observe an unusual number of MM cases in WTC responders under 45 years. This finding underscores the importance of maintaining surveillance for cancer and other emerging diseases in this highly exposed population.* (J Occup Environ Med. *2009;51:896–902*)

The destruction of the World Trade Center (WTC) on September 11, 2001, the fires that burned for the next 3 months, and the subsequent demolition and reconstruction at Ground Zero, the former site of the twin towers, produced an extraordinarily complex mix of airborne pollutants.[1–4] Polycyclic aromatic hydrocarbons, asbestos, and microscopic shards of glass were abundant. Airborne carcinogens—most notably benzene and polycyclic aromatic hydrocarbons as well as polychlorinated biphenyls, other organochlorines, dioxins, and furans—were present in measurable quantities, especially in the first 24 to 48 hours after the attacks. The principal source of benzene was the 91,000 L of jet fuel released from the two airplanes that hit the towers.

Rescue, recovery, and reconstruction workers as well as volunteers at Ground Zero were exposed to these airborne pollutants. Heaviest exposures occurred in the first days after the attacks, and workers engulfed in the dust cloud on September 11 sustained the most extreme exposures.[4] Governmental failure to require respiratory protection further increased inhalation exposures. All the workers at the site were exposed to great psychological stress.

Medical screening and treatment of 9/11 responders began within weeks of the attacks. Physicians at the Mount Sinai School of Medicine documented increased incidence of wheeze, cough, and shortness of breath in Ironworkers who had rushed to Ground Zero.[5] Investigators at the Fire Department of New York (FDNY) documented exposure-related

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increases in persistent cough, termed "World Trade Center cough," among firefighters.[6] Federal funding for medical screening became available in Spring 2002. Additional funding in Spring 2004 permitted substantial program expansion. To date, more than 40,000 workers and volunteers who served at Ground Zero have been screened and followed up through medical programs supported by the National Institute for Occupational Safety and Health at the New York/New Jersey consortium and FDNY. Health problems noted in these men and women include cough, wheeze, new-onset asthma, refractory sinusitis, vocal cord dysfunction, diminished lung capacity, pulmonary fibrosis, sarcoid-like granulomatous disease, gastroesophageal reflux disorder, posttraumatic stress disorder, and depression.[6–14] Follow-up and treatment continue for these men and women.

An important unanswered question is whether cancers or other chronic diseases will arise among 9/11 responders as a consequence of their occupational exposures to carcinogens at Ground Zero. Definitive resolution of this issue will require decades because of the long latency of many occupational cancers, especially those caused by asbestos. The WTC Medical Monitoring and Treatment Program (MMTP) has developed a web-based system for live data capture, supplemented by systematic reviews of all clinical databases to identify possible cases of cancer and other health outcomes of interest.

We report here on eight histopathologically confirmed cases of multiple myeloma (MM) that have arisen since September 11, 2001, among WTC responders seen in the New York/New Jersey consortium. Of note, four of these eight cases occurred in responders younger than 45 years. Three of these four arrived at Ground Zero on September 11, the day of heaviest exposure.

The Population at Risk

Controversy has surrounded calculation of the number of workers and volunteers who served at Ground Zero. A fundamental problem was that no records were kept of attendance at the site. Accurate information is available on the numbers of FDNY firefighters and paramedics who served, but information on virtually all other groups is fragmentary. A second problem is that the various programs following responders' health use differing definitions of eligible service, with a higher duration of exposure required for entry into the New York/New Jersey consortium than into the FDNY-based program or the New York City WTC Registry.[6,15] An early estimate was that 50,000 workers and volunteers served at Ground Zero.[4] In retrospect, however, this estimate appears low. Brackbill et al[15] calculated that as many as 90,000 workers and volunteers were present, but this estimate contains substantially inflated numbers reported by volunteer organizations and almost certainly overestimates the true reality. Given that nearly 30,000 eligible individuals have made at least telephone contact with the WTC MMTP and that another 15,000 have enrolled in the FDNY-based program, we have estimated that between 60,000 and 70,000 responders, who would have met eligibility criteria, were present at the site.[16]

The New York/New Jersey Consortium WTC MMTP

The goal of the monitoring component of the WTC MMTP program is to provide standardized screening examinations to all eligible responders. A follow-up examination is now provided every 12 months to monitor and track these eligible participants. A detailed description of this program has been published elsewhere, along with the eligibility criteria for inclusion in the program.[7]

As there was no systematic roster of non-FDNY WTC workers and volunteers from which the WTC MMTP could encourage participation and thus no direct way of calculating accurate prevalence estimates for the total responder population, the WTC MMTP has established an active patient tracking and retention program. This effort is designed to ensure that all eligible individuals are aware of the program, and participants who have received their first examination continue to come in for subsequent monitoring examinations. In addition, responders have been urged to report new conditions diagnosed between examinations to the program call center staff or to their WTC MMTP treating physician.

Examination Eligibility

Any responder who had been registered as eligible for participation in the WTC MMTP as of September 10, 2007, for whom data were available on age and gender was eligible for inclusion in this study.

Case Identification and Ascertainment

Cases of MM were identified in a number of ways. Patients are asked to self-report any diagnosed conditions to a WTC MMTP clinician during a baseline, monitoring, or treatment visit. They are asked structured questions during each visit inquiring about cancer diagnoses in their monitoring examinations. Registered patients may also call the WTC MMTP call center to report a new diagnosis between examinations. After a possible case is identified, the patient's records are reviewed, and the patient is contacted to gather detailed information about their diagnosis. If the patient had not yet had an evaluation, patient consent for authorizing the release of full medical records from the primary or treating physician is also collected. For each case, presented here, a full review of each individual's WTC MMTP examination records and medical records from the treating oncologist was conducted including review by a hematologist (KT). Diagnostic crite-

ria were based on the presence of bone marrow plasmacytosis (abnormal plasma cells) as per the World Health Organization and Mayo Clinic diagnostic criteria (Tables 1 and 2).[17,18] The date of diagnosis was based on the first bone marrow biopsy that showed the presence of abnormal plasma cells.[17]

Identification of MM Cases in Eligible Responders From September 11, 2001, to September 10, 2007

We examined charts and contacted physicians for responders who reported a diagnosis of MM at one of their monitoring visits, responders who alerted the program of a diagnosis of MM via phone or e-mail, and responders whose WTC MMTP monitoring physicians or outside physician reported a diagnosis of MM to the program. Confirmatory medical records were obtained and reviewed by a hematologist (KT). Exposure information was obtained by in-person or telephone interviews (for those cases who were too ill to travel) using a standardized exposure assessment instrument used for all WTC MMTP patients.

Table 3 lists the age, occupation, dates of diagnosis and of registration in the Program, and certain exposure information (arrival date at cleanup and location of work at site) for the eight confirmed cases of MM. We give additional detail for the four cases whose age at diagnosis was less than 45 years.

Table 4 gives the number of cases of MM in 5-year age intervals and contrasts them with the expected numbers, based on three sources: New York City, New York State, and Surveillance Epidemiology and End Results (SEER).[19] Expected values were based on multiplying the age and gender-specific rates noted in the standard populations by the number of responders in the different age and gender subgroups, and then multiplying those numbers for the 6 years of follow-up.

Clinical Cases Under 45 Years of Age

Patient 1

The patient is an African American male who worked as a law enforcement officer to secure the perimeter of Ground Zero. He was diagnosed with MM in 2005 at the age of 34 years. He was not present in lower Manhattan on 11 September, 2001. He worked adjacent to the WTC pile/pit for approximately 12 days from November 2001 through May 2002. He is currently employed as a law enforcement officer. In the course of his work, he reports being exposed to asbestos, diesel exhaust, dust (general), steel dust, and noise. His medical history includes papillary thyroid cancer, which was diagnosed and treated with a total thyroidectomy and radioactive iodine in 2005.

At the time of his first WTC MMTP examinations in March 2003, the patient was anemic with low serum iron levels. During his second WTC MMTP examinations in June 2005, he was again anemic and had thrombocytosis but no evidence of iron deficiency anemia. Urinalysis was also positive for protein. A bone marrow biopsy was performed in December 2005, which showed moderate plasmacytosis (15% to 20%) with kappa light chain restriction and an increase in CD138 plasma cells. Immunofixation showed no monoclonal bands, and protein electrophoresis showed a normal pattern. A 24-hour urine collection found 113 mg/24 hours urine protein. The patient was diagnosed with asymptomatic MM in December 2005.

A repeat bone marrow biopsy was performed in February 2006, which revealed a normal cellular bone marrow with a plasmacytosis of around 10% with slight increase in free kappa light chains and no end organ damage. A skeletal survey was also carried out, which showed no lytic lesions. A baseline magnetic resonance imaging (MRI) of the total spine was also conducted in April 2006 and no abnormalities were found. All these results confirmed the diagnosis of free kappa light chain MM. At his recent WTC MMTP examination, he reported taking the following medications: levothyroxine, atorvastatin, telmisartan, and pamidronate.

TABLE 1
Major and Minor Criteria[17]

Major Criterion	
	Marrow plasmacytosis with ≥30% plasma cells
	Plasmacytomas on tissue biopsy
	M component or monoclonal globulin spike on serum electrophoresis: IgG >3.5 g/dL, IgA >2 g/dL, urine >1.0 g/24 hr of Bence-Jones protein
Minor Criterion	
	Marrow plasmacytocis (10%–30%)
	M-component present but less than above
	Lytic bone lesions
	Reduced normal immunoglobulins (<50% normal)-IgG <600 mg/dL, IgA <100 mg/dL, IgM <50 mg/dL

The diagnosis of MM is confirmed when at least one major and one minor criterion or at least three minor criteria are present.

TABLE 2
Mayo Clinic Criteria for Diagnosis of MGUS (Monoclonal gammathopathy of undetermined significance), SMM (Smoldering multiple myeloma), IMM (Indolent multiple myeloma), and MM[18]

MGUS	Serum monoclonal protein <3 g/dL and bone marrow plasma cells <10% and absence of anemia, renal failure, hypercalcemia, and lytic bone lesions
SMM	Serum monoclonal protein ≥3 g/dL and/or ≥10% bone marrow plasma cells and absence of anemia, renal failure, hypercalcemia, and lytic lesion
IMM	Presence of a serum/urine monoclonal protein, bone marrow plasmacytosis and mild anemia or few small lytic bone lesions, and absence of symptoms
MM	Presence of serum/urine monoclonal proteins bone marrow plasmacytosis and anemia, renal failure, hypercalcemia, or lytic bone lesions; patients with primary systemic amyloidosis and ≥30% bone marrow plasma cells are considered to have both MM and amyloidosis

TABLE 3
Demographic and Clinical Characteristics of MM Cases

Pt No.	Age (in yr) at Diagnosis	Occupation	Arrival Date at WTC Site	Location of Work at WTC Site	Date of Diagnosis	Date of Registration
1	34	Law enforcement	14 November, 2001	Adjacent to the pile/pit	December 2005	May 2003
2	37	Law enforcement	11 September, 2001	Pile/pit, Landfill, OCME and south of Canal Street	March 2007	April 2004
3	40	Law enforcement	11 September, 2001	Landfill	April 2005	February 2003
4	43	Law enforcement	11 September, 2001	South of Canal Street	October 2004	June 2007
5	51	Manager	11 September, 2001	Pile/pit	August 2003	June 2007
6	61	Counselor	15 October, 2001	Adjacent to the pile/pit	September 2005	June 2007
7	68	Engineer	11 September, 2001	Adjacent to the pile/pit	August 2006	July 2006
8	71	Health professional	12 September, 2001	Adjacent to the pile/pit	March 2007	November 2006

TABLE 4
Observed vs Expected Cases of Multiple Myeloma by Age

Total Age Group (yr)	Observed	Expected New York City	Expected New York State	Expected SEER
<30	0	0.01	0.01	0.01
30–34	1	0.08	0.09	0.11
35–39	1	0.39	0.40	0.29
40–44	2	0.62	0.69	0.59
<45	**4**	**1.09**	**1.22**	**1.00**
45–49	0	1.17	1.04	0.91
50–54	1	1.40	1.29	1.04
55–59	0	1.47	1.27	1.10
60–64	1	0.94	0.84	0.79
65–69	1	0.42	0.41	0.39
70–74	1	0.18	0.18	0.18
>75	0	0.10	0.10	0.10
Total	**8**	**6.77**	**6.35**	**5.55**

Patient 2

The patient is a White male who worked as a law enforcement officer at the WTC site. He was diagnosed with MM in 2007 at the age of 37 years. He worked at the WTC pile/pit, the Staten Island Landfill, in areas south of Canal Street, and at the OCME. He worked for approximately 218 days from September 11, 2001, through May 2002. He was present on 9/11 and was caught in the dust cloud. He usually ate on-site and was sent home for only 5 to 6 hours a day for the 2 months following 9/11. He has been working in law enforcement since he was 19 years old. He has family history of prostate and colon cancer.

The patient had an increased serum creatinine level, found in routine blood work at the end of 2006. The patient reported light headedness and severe weakness and lack of energy in the beginning of 2007. He also noted foaming urine and urinary frequency in March 2007. He was referred to a kidney specialist. A kidney biopsy was performed in March 2007, which revealed cast nephropathy with lambda light chain on immunopathology, mild-moderate diffuse interstitial fibrosis, and tubular atrophy. A bone marrow biopsy performed in March 2007 showed 65% to 70% cellularity with 40% plasma cells. Flow cytometry revealed a monoclonal IgA lambda plasma cell population. The plasma cells were CD138 positive and lambda light chain restricted. Serum protein electrophoresis (SPEP) and Quantitative immunoglobulins analysis revealed three peaks consistent with paraprotein peaks, elevated IgA, and reduced IgM and IgG. A 24-hour urine protein was 6165 g/d with 80% Bence Jones Proteinuria. Serum immunofixation electrophoresis (IFE) also revealed an IgA lambda with free lambda. A MRI of the thorax and lumbar spine showed a focal lesion with in the L4 vertebral body and posterior element of L2. A chest radiograph showed lytic bone disease in the clavicle and/or sternum.

The patient was diagnosed with IgA lambda MM in March 2007. Amyloid deposits were seen on fine needle aspiration of abdominal fat conducted in September 2007. The patient received chemotherapy and a stem cell transplant in September 2007. The patient was unable to come in for any WTC MMTP examinations because he was too ill to travel, and in June 2007, a program physician interviewed him over the phone using the standardized examination questionnaires.

Patient 3

The patient is a White male whose activities at Ground Zero included sifting and morgue work. He was diagnosed with MM in 2005 at the age of 40 years. He reported having been present in lower Manhattan on September 11, 2001, but was not engulfed in the dust cloud. He stated that he had worked at the Staten Island Fresh Kills Landfill for 111 days from September 11, 2001, through February 2002. The patient worked as law enforcement officer, which is also his current profession. He reports being exposed to dust (general and wood), ergonomic risk factors, heat/cold stress, noise, and

smoke (noncigarette) in relation to his occupation.

At the time of his first MMTP examination in March 2003, the patient had a mildly elevated serum total protein level. He was diagnosed with IgG kappa light chain MM in April 2005. Treatment of MM included chemotherapy with a regimen of thalidomide, decadron, and radiation and tandem autologous stem cell transplants.

He reported his diagnosis of MM during his second monitoring visit in 2006 and provided the monitoring physician with copies of his medical records. At that time, the patient was anemic and had persistent elevated total protein levels.

Patient 4

The patient is a White male who worked as a law enforcement officer at the WTC site. He performed rescue and recovery efforts at the WTC site. He was diagnosed with MM in 2004 at the age of 43 years. He reported having worked south of Canal Street for approximately 14 days in September. He retired from his work as a law enforcement officer in 2004. He has a family history of head, neck, and stomach cancer.

A routine urinalysis in 2004 revealed proteinuria and hematuria. A computed tomography scan of the abdomen and pelvis performed in September 2004 showed a left renal cyst and pleural thickening. A follow-up computed tomography of the chest showed multiple lytic lesions within the ribs with extrapleural para-osseous soft tissue masses. Anemia and hypoalbuminemia were observed on blood analysis. A bone marrow biopsy was performed in October 2004, which showed hypercellular bone marrow (80% cellularity) with diffuse interstitial infiltrate of plasma cells of about 35%, consistent with a diagnosis of myeloma. SPEP was negative for an M-spike. Immunofixation and Quantitative Immunoglobulin analysis also appeared to be reduced with a low IgM and free lambda and kappa chains. A skeletal survey showed lytic lesions in the rib, skull, and spine. The patient was diagnosed with lambda light chain MM with multiple bony lesions in October 2004. He was treated with chemotherapy and stem cell transplant. He received a tandem transplant in 2005 and was in complete hematological remission. The patient did not come for any WTC MMTP examinations. He contacted a program physician in Spring 2007.

Discussion

We report here on eight cases of MM that were diagnosed and reported to the WTC MMTP between 2004 and 2007, in WTC responders who were seen through the New York/New Jersey consortium. MM is typically a disease of the elderly. We report the occurrence of these cases to guide physicians caring for 9/11 responders and to alert clinicians that periodic screening of responders for health conditions, such as MM, may be prudent. Atypically, four of the eight cases of MM seen here occurred in responders younger than 45 years. These cases occurred in a population of 28,252 responders who registered for the New York/New Jersey consortium WTC MMTP. Of this population, 24,074 were men, with 17,841 younger than 45 years, and 4178 were women, with 3096 younger than 45. Overall, 74% of our patient population are younger than 45 years as of September 11, 2001. We observed four cases under age 45, while the three sources predict from 1.0 to 1.2 cases in this young age group, based on three sources: New York City, New York State, and SEER.[19] The four cases described in this article were all members of law enforcement and had no other occupational exposures that might have increased the risk for developing MM.

MM is the second most common hematological malignancy in the United States, after Non-Hodgkin's Lymphoma.[20] The overall incidence of MM is 4.4/100,000 per year, and incidence rates in males are 1.5 times greater than those in females.[21,22] The median age of diagnosis of MM is 71 years and about 99% of cases are seen in people older than 40 years.[22,23] Risk of MM was observed to be 10-fold greater in those 70 to 74 years of age compared with those 45 to 49 years, according to the National Cancer Institute SEER program, 2005.[19,23]

Known risk factors for MM include the following: male gender and increasing age, African American race, obesity, a positive family history of lymphatohematopoietic cancer, and monoclonal gammopathy of undetermined significance.[22,24]

Currently, there are no studies evaluating the potentially carcinogenic effects of exposure to a complex mixture of substances comparable with that sustained by WTC responders.[18] However, it is known that many of the potential exposures at the WTC including benzene, paint and solvent vapors, aromatic hydrocarbons, polychlorinated biphenyls, dioxin, pesticides, engine exhaust, and metals have been associated with increased rates of myeloma in previous studies.[22,25–30]

Selection bias resulting from preferential enrollment of ill responders into the federally funded New York/New Jersey consortium WTC MMTP is potentially a problem in our data. Selection bias is not so great an issue if the total number of responders who served at Ground Zero is close to 50,000, given that the New York/New Jersey consortium and FDNY programs have now together evaluated nearly 45,000 responders. However, selection bias becomes a potentially greater issue as the estimated number of responders increases and the rate of participation in the New York/New Jersey consortium program therefore decreases. The possibility then exists that responders who would not otherwise have enrolled in the New York/New Jersey consortium WTC MMTP could have chosen to do so after symptoms of MM arose or after a physician outside of the program gave them a diagnosis of MM. On

the other hand, individuals who were diagnosed with MM and unaware of the program's existence or were too ill to contract the program might not have registered, which could underestimate the number of cases of myeloma seen. Our best estimate of the true number of WTC responders is 60,000 to 70,000.[16]

An additional concern is the possibility that our monitoring program was detecting MM cases more effectively than would have occurred in the comparison populations due to more intense medical evaluation than is typical for the general population, particularly in younger adults. Even if there is some acceleration in the diagnoses, which is caused by enrollment in the program, the condition would come to be diagnosed at a later time, and so there might be a shift toward somewhat younger ages at diagnosis in the WTC workers, but this would not produce a sustained increase in the rate of occurrence as workers are followed up over time.

African American race is considered a risk factor for MM. Our responder population has a smaller percentage of blacks than New York City as a whole. Because we have fewer responders at increased risk because of ethnic differences, the observed incidence of overall cases is somewhat more striking. In addition, our findings are very slightly understated because we ignored the 680 responders who registered via phone with unknown age (and two with unknown sex). None of them had MM.

The exact nature of the complex mixture of toxins released into the air on September 11, 2001, and, consequently, the extent and precise nature of the exposures sustained by workers and volunteers will never be fully known. However, based on extensive analysis of dust samples collected from sites around lower Manhattan after 9/11, it is certain that the air contained many known carcinogens. The combined effects of all the substances present at Ground Zero could interact to have new and unexpected health effects.

Because of the risk for new and possibly unexpected diseases that might manifest in the WTC worker and volunteer population in the coming years, it is essential to maintain an active disease surveillance initiative such as the program currently established by the WTC MMTP. To enhance case ascertainment within this program, we are in the process of establishing linkages with the New York State Cancer Registry. We are in the process of verifying an additional eight cases of myeloma that have been reported to us since September 2007; seven were reported prior to September 2008 and one was reported after that point. Two of these additional eight cases are under 45, two are between 45 and 50 years, two are between 50 and 55 years, and the additional two cases are above 55 years. We expect to report on the overall number of verified cases of myeloma in future publications.

Our motive in presenting these findings is to guide physicians who may be caring for 9/11 responders. Although it is too early to say whether the risk of MM is truly increased among WTC responders, we felt that it is important to report these cases, particularly, because MM is unusual in individuals younger than 45 years. The latency period that we have reported in these cases is significantly shorter than the latency period for MM as a result of benzene exposure or other organic solvents in the literature, ranging from 10 to 19 years in one study and more than 20 years in other studies.[30,27] Clinicians treating WTC responders should be aware that the age distribution of MM and other chronic diseases may be skewed in this population and be alert for emerging disease trends.

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