Waldenstrom's Macroglobulinemia: Search for Occupational Exposure

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Two cases of Waldenstrom's macroglobulinemia (WM) that occurred in employees from one university academic department were investigated using approaches for both cluster and single case investigation. Common personal characteristics and potential past hazardous exposures were evaluated. The patients shared a young age at diagnosis, worked in the same building, and had similar duration of time between first entering the building and diagnosis of WM. No evidence was found to support the original hypothesis that exposure to radioactive material could be related to the occurrence of WM. Although this investigation did not identify a common causal agent among two cases of a rare disease, investigations of disease clusters may be useful for developing etiologic hypotheses even when a full-scale epidemiologic study is not undertaken. Detailed descriptions of case characteristics can help generate ideas for further research.

Investigations of cases and of disease clusters have common features. Both have played a role in providing meaningful etiologic clues to many occupational diseases,[1] yet often are not considered within the realm of epidemiologic research.[2] Nonetheless, these investigations are an important responsibility of public health agencies.[3] Although protocols have been developed for public health agency response to cluster investigations,[4-6] systematic approaches for epidemiologic case investigation are not well established.[7] This report describes the investigation of two cases of a rare disease, Waldenstrom's macroglobulinemia (WM), that used existing approaches for cluster investigation and incorporated recently suggested techniques for case investigation. Because little is known about the causes of this disease, case reports can be useful in guiding etiologic research.

(In this investigation Waldenstrom's macroglobulinemia is considered as a type of cancer because of its similarity to some other cancers, such as chronic lymphocytic leukemia. In the international system for classifying diseases, however, Waldenstrom's macroglobulinemia is grouped with plasma cell disorders rather than with neoplastic diseases.[8])

In late 1991, the National Institute for Occupational Safety and Health (NIOSH) received a request for a health hazard evaluation from three employees of a social science department of a major university in the southeastern United States. The employees were concerned about a suspected cancer cluster among faculty and students in the department. Among 11 individuals diagnosed with various types of cancer between 1985 and 1990, were two cases of WM.

WM is one of a group of monoclo-

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nal neoplasms that develop from B-lymphocytes.[9] The disease primarily occurs in men over the age of 60.[10] About one new case in a population of 200,000 is detected each year.[11]

Little is known about the causes of WM. Autoimmune disorders and other immunologic abnormalities among close relatives of WM patients and a history of chronic biliary tract diseases and of diseases associated with chronic antigenic stimulation among WM patients have been reported.[10] The relationship between WM and occupational exposures has not been evaluated adequately. One epidemiologic study found no association between WM and a variety of occupational exposures, including those related to leukemia or lymphoma.[12] Three cases of WM in shoe repairers and one case in a bird breeder have been described.[11,13]

Methods

This investigation focused on (1) identifying potential past exposure to hazardous agents in the building where the two persons with WM were located and (2) describing personal characteristics common to the case subjects.

Characteristics of Building A

Before 1955, Building A was occupied by the biology (1937 to 1947) and geology (1947 to 1955) departments. Since 1955, the building has been occupied by various social science departments.

Before NIOSH involvement, the university conducted assessments of indoor air quality, organic chemicals in the soil around the building and in the air within the building, and radiation. The results from wipe samples of wall tiles indicated very low, but statistically significant, radiation counts above background in several rooms scattered throughout the building. Because we considered radioactive material to be the only agent that would have been present in Building A during the time period relevant to the onset of disease and that could have provided a plausible explanation for the occurrence of WM, we sought to determine whether research activities in Building A from 1940 to 1955 might have involved the use of any natural or artificially produced, long-lived radioactive materials. A history of research activities in Building A was documented from university records, including (1) records of the radiation safety office, (2) contents of appropriate doctoral dissertations and masters' theses, and (3) annual departmental reports, which list faculty publications and presentations.

Case Subject Characteristics

Medical records were obtained to confirm the diagnosis of the case subjects (one living, one deceased). Information about temporal, geographic, and personal characteristics was obtained from departmental records and from telephone interviews and self-administered questionnaires completed by case subject 1 and the spouse of case subject 2. The spouse was married to the case subject throughout the time he was associated with the department; she indicated that she discussed some of the information we requested with the parents of the decedent to ensure that all available information was reported.

Results

Characteristics of Building A

The radiation safety office provided us with lists of authorized radioisotope users, film badge records, waste disposal records, and past Atomic Energy Commission license approvals. We found no information about the use of radioactive materials before 1960.

The Dissertation Abstracts computerized data base did not include any doctoral dissertations in biology (zoology, bacteriology, botany), archaeology, or geology between 1940 and 1955. In a manual search of approximately 450 masters' theses for this same time period, we did not discover any use of radioactive materials in Building A. No evidence of the use of radioactive materials was found among faculty presentations and publications listed in the annual reports.

Case Subject Characteristics

Medical records documented clinical and laboratory findings consistent with the diagnosis of WM for both cases, including (1) a monoclonal IgM spike, (2) symptoms associated with a hyperviscosity syndrome, and (3) large numbers of lymphocytes in bone marrow aspirate. Personal and building-related characteristics of the case subjects are summarized in Table 1. Young age at diagnosis, work in the same building, and similar duration of time between first entering the building and diagnosis of WM are the most remarkable features shared by the cases.

Discussion

Public health agencies have reported that cluster investigations (which frequently include epidemiologic and environmental components) are largely unproductive in linking disease occurrences to documented exposures.[15,16] Nonetheless, these agencies have a duty to respond in some way to reports of suspect cancer clusters. Such response can help build public trust.[17] Although the past occurrence of disease often cannot be explained, cluster investigations can produce information about future risks due to current exposures. Documentation of the absence of current exposures often is reassuring to affected workers or residents. Documentation of the presence of current exposures can lead to recommendations to reduce future risk.

Many agencies have developed standard protocols for determining whether and how far cluster investigations should proceed.[4–6,16,17] Most begin with a preliminary review of readily available information about the cases (eg, type of cancer, dates of diagnosis, date of first employment or residency in an area, and age, race, sex, and vital status of case subjects) and about the environment in which they work or live. This information usually is obtained from the person(s) who reported the cluster and, at this stage, often is not verified. To the extent possible, this information is reviewed to (1) assess whether there is an unusual distribution of types of

TABLE 1
Characteristics of Two Persons with Waldenstrom's Macroglobulinemia in an Investigation of a Suspected Cancer Cluster in a University Academic Building

Characteristic	Case 1	Case 2
Gender	Male	Male
Place of birth	United States	North Africa
Race	White	White
Age at diagnoses (y)	44	47
Year entered Building A	1970	1965
Years between entering Building A and diagnosis	21	20
Years in Building A	4	20
Exposure to chemical or physical agents		
Occupational	No	No
Hobby	No	No
Exposure to animals in household	Yes*	Yes†
History of immune disorders or allergy	No	Yes‡
History of chronic biliary tract disease	Yes	No
Family history of immune disorders	No	No
History of cancer in first-degree relatives		
Any cancer§	Yes	Yes
Hematopoietic cancer	No	No

* Dogs.
† Dogs, cats, chickens, goats.
‡ Chronic sinusitis.
§ Case 1, grandparent, esophagus; case 2, grandparent, stomach; parent, larynx.

cancer or of the age or gender of the persons with cancer, (2) determine whether the cancers have occurred with sufficient latency since first exposure, and (3) identify a potential causal factor. Many investigations do not proceed beyond the preliminary review. If further investigation is warranted, an epidemiologic study frequently is considered. Even without a traditional epidemiologic study, however, further investigation can provide etiologic clues, particularly for rare diseases for which risk factors have not been delineated, and can generate valuable information about future risks from continuing exposures. Case investigations such as that described in this report should be given consideration in the decision-making process.

The premise for the investigation of WM described in this report was that in-depth case evaluation might lend support to hypotheses derived from prior case reports or suggest new avenues of research. The methods used in this investigation incorporated many of the recommendations of Armenian[7] for case investigation, including (1) orienting the case as to time, place, and personal characteristics, (2) collecting standard data about epidemiologic characteristics, (3) obtaining family history and a history of past illnesses, and (4) exploring the likes and dislikes of the patient.

Neither of the persons with WM in this investigation had occupational exposure to chemical or biological agents similar to those identified in previous case reports.[11,13] The similarities between the cases in the length of time from first entering the building to diagnosis and a younger age at diagnosis than is usually described for WM were consistent with the possibility that an exposure in the building was causally related to the disease. Although preliminary information suggested exposure to ionizing radiation, we found no indication that natural or artificially produced, long-lived radioactive materials were present during a 25-year period before the earliest time either of the persons with WM began working in the building. Information about current levels of radiation in and around the building was collected and reported to building occupants to assure them that they currently are not exposed to high levels of radiation.[18]

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References

1. Fleming LE, Ducatman AM, Shalat SL. Disease clusters: a central and ongoing role in occupational health. *J Occup Med.* 1991;33:818–825.
2. Rothman KJ. A sobering start for the cluster busters' conference. *Am J Epidemiol.* 1990;132(Suppl):S6–S13.
3. Rothenberg RB, Steinberg KK, Thacker SB. The public health importance of clusters: a note from the Centers for Disease Control. *Am J Epidemiol.* 1990; 132(Suppl):S3–S5.
4. Fiore BJ, Hanrahan LP, Anderson HA. State health department response to disease cluster reports: a protocol for investigation. *Am J Epidemiol.* 1990; 132(Suppl):S14–S22.
5. Devier JR, Brownson RC, Bagby JR, Clarson GM, Crellin JR. A public health response to cancer clusters in Missouri. *Am J Epidemiol.* 1990; 132(Suppl):S23–S31.
6. Anonymous. Guidelines for investigating clusters of health events. Recommendations and Reports. *MMWR.* 1990;39/No. RR-11.
7. Armenian HK. Case investigation in epidemiology. *Am J Epidemiol.* 1991;134: 1067–1072.
8. World Health Organization. *Manual of the International Classification of Diseases, Injuries, and Causes of Death*, 9th Revision. Geneva, Switzerland: World Health Organization; 1977.
9. Longo D. Plasma cell disorders. In: Wilson JD, Braunwald E, Isselbacher KJ, et al, eds. *Harrison's Principles of Internal Medicine*, Volume 2. New York: McGraw-Hill, Inc; 1991:1410–1417.
10. Blattner WA. Multiple myeloma and macroglobulinemia. In: Schottenfeld D, Fraumeni Jr, JF, eds. *Cancer Epidemiology and Prevention.* Philadelphia: W.B. Saunders Co; 1982:795–813.
11. Williamson LM, Greaves M, Waters JR, Harling CC. Waldenstrom's macroglobulinaemia: three cases in shoe repairers. *Br Med J.* 1989;298:498–499.
12. Linet MS, Humphrey RL, McCaffrey LD, Mehl ES, Dietz MS. A population-based case-control and family study of Waldenstrom's macroglobulinemia [Abstract]. *Am J Epidemiol.* 1988;128:938.
13. James JM, Brouet JC, Orvoenfrija E, et al. Waldenstrom's macroglobulinemia in a bird breeder: a case history with pulmonary involvement and antibody activity of the monoclonal IgM to canary's droppings. *Clin Exp Immunol.* 1987;68: 397–401.
14. Anonymous. *A Citizen's Guide to Ra-*

don. Washington, DC: US Environmental Protection Agency, Office of Air and Radiation; 1986. OPA-86-004.
15. Caldwell GG. Twenty-two years of cancer clusted investigations at the Centers for Disease Control. *Am J Epidemiol.* 1990;132(Suppl):S43–S47.
16. Schulte PA, Ehrenberg RL, Singal MS. Investigation of occupational cancer clusters: theory and practice. *Am J Public Health.* 1987;77:52–56.
17. Bender AP, Williams AN, Johnson RA, Jagger HG. Appropriate public health responses to clusters: the art of being responsibly responsive. *Am J Epidemiol.* 1990;132(Suppl):S48–S52.
18. Health Hazard Evaluation Report: University of Georgia, Athens, Georgia. Cincinnati, OH: US Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, NIOSH Report No. HETA 91-360-2226; 1992.

Mozart—A Quick High for Our IQ?

Those who hope to seem smarter by listening to Mozart may be on to something—at least temporarily. Researchers at the Center for the Neurobiology of Learning and Memory at the University of California–Irvine have determined that 10 minutes of listening to a Mozart piano sonata raised the measurable IQ of college students as much as 9 points. The effect, however, lasted barely longer than the echo of the piano chords: The IQ boost dissipated within 15 minutes, the team reported in yesterday's edition of the journal *Nature.*

The researchers suggested that classical music may enhance abstract reasoning, such as that involved in mathematics, by reinforcing certain complex patterns of neural activity. They suspect that the complexity of the music is the key. Simpler, repetitive rhythms of rock or minimalist New Age jazz may actually interfere with abstract reasoning.

The research grows out of theoretical neurobiology and ideas about how different parts of the brain may communicate with each other. "There is a common language the different parts of the brain use to communicate," said Gordon Shaw, a physics professor who was involved in the research. "There are certain neurological firing patterns that occur when people are doing high levels of abstract reasoning. We take those as describing the internal language of the brain. The music presumably excites these same very structured patterns," he said.

In the study, 36 college students were given standard IQ tests after listening to Mozart's Sonata for Two Pianos in D Major, a recorded relaxation tape, or meditating in silence for 10 minutes. Each student was tested after each listening exercise. Each student's test score was higher after listening to the classical passage, the researchers reported.

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