

The study findings, taken in conjunction with the known myocardial abnormalities of fibrosis and conduction-system degeneration, make it probable that acute unstable arrhythmias were responsible for the majority of sudden deaths. The study was a multicenter investigation, and the ability to request autopsies was limited.

We agree that progressive skeletal-muscle weakness leading to respiratory failure is a significant issue in the care of patients with myotonic dystrophy. Respiratory failure was the most common cause of death in our study. Whether respiratory status had a role in the initiation of the event leading to sudden death is not clear. As detailed in our article, the presence of severe muscular weakness did affect the patients' and caregivers' decisions regarding the treatment of unstable arrhythmias. On the basis of our study findings, we agree that a yearly noninvasive evaluation, including assessment for atrial tachyarrhythmias and severe conduction abnormalities on the ECG, will aid in determining the risk of sudden death. We do not agree that nonmortality outcomes from nonrandomized observations in a referred population have proved the diagnostic usefulness of invasive electrophysiological studies or the therapeutic benefit of prophylactic pacemakers in the management of sudden death in patients with myotonic dystrophy.¹⁻³

The cohort analysis by Hermans and colleagues provides support for our finding that sudden death is a common cause of death among patients with myotonic dystrophy type 1 and that pacemakers may not prevent sudden death. We understand the rationale behind their recommendation for prophylactic ICDs. However, we

believe that the population of patients with myotonic dystrophy type 1 is of sufficient size and clinical complexity that a prospective mortality assessment of the benefit of ICDs is indicated. With the worldwide interest in evaluating methods to prevent sudden death in patients with myotonic dystrophy type 1, a multinational trial would be optimal. We encourage investigators providing care for patients with myotonic dystrophy type 1 to design and implement such a necessary trial.

Vrtovec and Haddad question whether QT prolongation detected on ECG predicts sudden death in patients with myotonic dystrophy type 1. We found no independent association between markers of prolonged repolarization and sudden death.

Sovari and Dudley hypothesize that TGF- β 1 could serve as a biomarker for sudden death in patients with myotonic dystrophy type 1. We did not evaluate TGF- β 1 and have seen no published data.

William J. Groh, M.D., M.P.H.

Deepak Bhakta, M.D.

Robert M. Pascuzzi, M.D.

Indiana University
Indianapolis, IN 46202
wgroh@iupui.edu

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Case 19-2008: Merkel-Cell Carcinoma

TO THE EDITOR: In the Case Record, Busse et al. (June 19 issue)¹ discuss a case of Merkel-cell carcinoma in a patient with human immunodeficiency virus (HIV) infection. We disagree with the discussants about similarities between Merkel-cell carcinoma and small-cell lung cancer, particularly with respect to recommendations for adjuvant chemotherapy. Busse et al. note, "Current guidelines published by the National Comprehensive Cancer Network [NCCN] state that Merkel-cell carcinomas, regardless of stage,

should be treated according to paradigms established for small-cell lung cancer." In fact, adjuvant chemotherapy is not recommended by the NCCN for Merkel-cell carcinoma, since "available retrospective studies do not suggest prolonged survival benefit for adjuvant chemotherapy."² Furthermore, important clinical and molecular data refute the authors' assertion that the biologic features of Merkel-cell carcinoma "appear to be equivalent to those of a small-cell carcinoma of the lung." First, Merkel-cell carcinoma is 10 to 30

times as common in immunosuppressed patients as in those who are not immunosuppressed.³ Second, a polyomavirus is present in 80% of patients with Merkel-cell carcinoma.⁴ Third, Merkel-cell carcinoma is essentially limited to whites (98% of cases), and most cases (80%) involve sun-exposed sites.³ Finally, key biologic features differ between the two cancers, including activation of the mitogen-activated protein (MAP) kinase pathway, which occurs in approximately 50% of patients with small-cell lung cancer but in less than 5% of those with Merkel-cell carcinoma.⁵

Bianca D. Lemos, M.D.

University of Washington
Seattle, WA 98109

Siegrid S. Yu, M.D.

University of California, San Francisco
San Francisco, CA 94115

Paul Nghiem, M.D., Ph.D.

Fred Hutchinson Cancer Research Center
Seattle, WA 98109
pnghiem@u.washington.edu

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TO THE EDITOR: Busse et al. discuss a case of stage III Merkel-cell carcinoma. Treatment resulted in good palliation before death from metastatic disease. Contrary to the authors' statement, the current NCCN guidelines do not recommend that patients with Merkel-cell carcinoma, regardless of stage, "be treated according to paradigms . . . for small-cell lung cancer."¹ Surgery remains the primary treatment approach for Merkel-cell carcinoma, since there are no data that clearly demonstrate an improvement in survival with chemotherapy.² The discussants' general comments on the management of stage II Merkel-cell carcinoma are not supported by current data and contemporary practice. Local disease control can be achieved with surgical margins of 1 to 2 cm rather than 2 to 3 cm, as suggested, and the

statement that Merkel-cell carcinoma must be treated as a systemic disease is inconsistent with survival rates for node-negative patients treated with local therapy alone, which exceed 90%.³ Sentinel lymph-node biopsy in patients with clinical stage I or II disease provides important prognostic information and spares those with negative results the morbidity associated with unnecessary lymphadenectomy or regional radiation therapy.⁴

Sandra L. Wong, M.D.

Christopher D. Lao, M.D.

Christopher K. Bichakjian, M.D.

University of Michigan
Ann Arbor, MI 48109
wongsl@umich.edu

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THE DISCUSSANTS REPLY: Lemos et al. and Wong et al. raise interesting points. With respect to NCCN guidelines, chemotherapy is listed as a treatment option for any node-positive or metastatic disease, and the NCCN panel does recommend the platinum-based combinations that are used for small-cell lung cancer.¹ Lemos et al. cite evidence that Merkel-cell carcinoma is not small-cell lung cancer, and as we learn more about Merkel-cell carcinoma and its molecular fingerprints, it may well turn out to be a distinct entity. However, we contend that there are more than enough similarities (histologic appearance, metastatic incidence, pattern of spread, and sensitivity to radiation and chemotherapy) to warrant the same functional categorization. At the moment, none of these molecular markers serve as a prognostic indicator or as a guide to therapy, and we believe that it is appropriate to consider treating high-risk Merkel-cell carcinoma and small-cell lung cancer in a similar fashion.

Most patients with clinical stage I disease (primary lesion, ≤ 2 cm in diameter; node-negative) do well with surgery or surgery plus radiation therapy and have a 5-year disease-specific survival rate of 81%; the rate is 68% for patients with

clinical stage II disease (primary lesion, >2 cm; node-negative).² These rates are much lower than the 90% rate cited by Wong et al. Unfortunately, the majority of patients do not fare even this well, since the overall 5-year survival rates range from 30 to 64%.³ In our opinion, this warrants more comprehensive therapy than surgery alone.

There are several issues we wished to put forward as points of consideration regarding the management of Merkel-cell carcinoma, recognizing that some may be controversial. First, there is a high degree of regional and systemic spread despite a seemingly limited primary cancer. Second, the sensitivity of gross regional disease to combined therapy suggests that surgery may not be necessary. Third, an aggressive regimen of combined treatment approaches can be delivered even in the setting of HIV infection and low CD4 cell levels. Fourth, radiation techniques can

make a difference in acute and late morbidity. One point on which there is no disagreement is that we all base our opinions and treatment recommendations on a paucity of clinical information and formal clinical trials for a relatively rare but interesting disease.

Paul M. Busse, M.D., Ph.D.

John R. Clark, M.D.

Massachusetts General Hospital

Boston, MA 02114

pbusse@partners.org

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Antigenically Distinct MF59-Adjuvanted Vaccine to Boost Immunity to H5N1

TO THE EDITOR: Antigenically distinct avian influenza A (H5N1) viruses are widely dispersed.¹ Clade 1 H5N1 viruses previously predominated in Indochina. Indonesian, Eurasian, and African viruses are clustered in a clade 2 group, with antigenically distinct sublineages. Clade 0 viruses caused influenza outbreaks in Hong Kong in 1997 but have not been isolated since then. To reduce shortfalls in vaccine supply at the onset of the next pandemic, advance stockpiling of vaccine has been suggested. Because of antigenic evolution of H5N1, current vaccines may be suboptimally matched to the actual pandemic virus. Proactive priming may induce immune memory, allowing low-dose vaccination to induce rapid cross-protection when needed.

We report on an open-label study conducted from June through August 2007 at Leicester Royal Infirmary, Leicester, United Kingdom (for details, see the Supplementary Appendix, available with the full text of this letter at www.nejm.org). Two 7.5- μ g doses of MF59-adjuvanted, surface-antigen vaccine against clade 1 A/Vietnam/1194/2004 (NIBRG-14) (Novartis) were administered by intramuscular injection 21 days apart to subjects who had been vaccinated (primed) with clade 0 H5 vac-

cine at least 6 years earlier. All primed subjects had received two doses of either MF59-adjuvanted or nonadjuvanted (plain) A/duck/Singapore/97 (H5N3) vaccine containing 7.5 to 30 μ g of hemagglutinin in studies conducted between 1999 and 2001.²⁻⁴ Some subjects had also received a booster dose 16 months after primary immunization.³ Antibody responses were detected with the use of neutralizing and hemagglutination-inhibition assays performed at the U.K. Health Protection Agency, with homologous clade 1 NIBRG-14 and heterologous clade 2.2 NIBRG-23 vaccine reference strains and by hemagglutination-inhibition assay at the Centers for Disease Control and Prevention with wild-type A/Vietnam/1194/2004 (clade 1), A/Indonesia/5/2005 (clade 2.1), A/Anhui/1/2005 (clade 2.3), and A/Turkey/15/2006 (clade 2.2) viruses (see the Supplementary Appendix for details).

Twenty-four subjects had received two or three doses of either plain or MF59-adjuvanted H5N3 vaccine, with subjects equally divided between the two groups. Thirty subjects were unprimed. Vaccines had acceptable side-effect profiles, and no serious vaccine-related adverse events were recorded. Serum samples were obtained immediately