demic. We further agree that a better understanding of this and other influenza pandemics at many levels, including epidemiology, virology, pathogenesis, host response, and the study of novel therapeutic modalities, including anti-inflammatory agents to augment the treatment of serious influenza infection, are important for pandemic planning.

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Does Contrast Enhancement Predict Survival in Progressive Multifocal Leukoencephalopathy?

To the Editor—I read with interest the recent article by Engsig et al. [1]. The authors used the lack of contrast enhancement on computed tomography (CT) or magnetic resonance imaging (MRI) scans to identify patients with progressive multifocal leukoencephalopathy (PML). They also reported that the only 2 patients with PML who developed immune reconstitution inflammatory syndrome (IRIS) after the initiation of highly active antiretroviral therapy (HAART) had no signs of contrast enhancement [1]. In patients with PML, MRI can detect more lesions than CT. In 1997, von Giesen et al. [2] included the lack of contrast enhancement on MRI scans as a diagnostic criterion for PML in HIV-positive patients. This feature helped distinguish PML from more common AIDS-defining diseases, such as toxoplasmosis and non-Hodgkin lymphoma. Actually, rare instances of PML with contrast enhancement on either CT or MRI scans have been reported since 1984 for both HIV-negative and HIV-positive patients [3–9]. In some cases these contrast-enhanced areas were shown to have causes other than PML (e.g., leukemic infiltrates [10]); however, in most cases they were areas of JC virus–associated demyelination.

Although some patients with PML who have contrast-enhancing lesions die [4], contrast enhancement may indicate an inflammatory response and, thus, herald immunologic elimination of virus, leading to improved survival [11]. In 1998, Berger et al. [12] showed that contrast enhancement, typically faint and peripheral, was seen on 10% of CT and 15% of MRI scans. In another study, the same group showed that contrast enhancement on radiographic images was observed for 3 (50%) of 6 long-term survivors, compared with 4 (8.9%) of 45 short-term survivors [13]. In 1999, Post et al. [14] showed that, in HIV-positive patients with PML, no MRI abnormalities statistically significantly correlated with patient survival in either univariate or multivariate analysis with the exception of mass effect, which was significantly associated with shorter survival.

Similarly, among 7 patients with PML (5 HIV-negative patients with hematological conditions and 2 HIV-positive patients), Küker et al. [15] encountered contrast enhancement only once after successful treatment, and it heralded clinical remission with elimination of virus from the cerebrospinal fluid. Nelson et al. [16] demonstrated that the pathological parenchymal blush and arteriovenous shunting seen angiographically in some patients with PML reflect small-vessel proliferation and perivascular inflammatory changes. Gray et al. [17] reported that contrast enhancement was seen for all 8 cases of IRIS occurring in patients with AIDS after immune restoration was induced by HAART; interestingly, PML is often exacerbated by IRIS in patients with AIDS.

In light of these data, it would be interesting to learn from Engsig et al. what the prevalence of contrast enhancement was among long-term survivors of PML versus PML progressors in their large cohort.

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Reply to Focosi

To the Editor—Focosi [1] has raised an interesting question that inspired us to reanalyze the data from our previous study [2]. We reviewed all computed tomography (CT) and magnetic resonance imaging (MRI) scan reports for all 47 patients with progressive multifocal leukoencephalopathy (PML). Seven patients had contrast enhancement described in at least 1 scan report. For 1 patient, vaguely hyperintense areas were observed on T1-weighted MRI scans after the administration of gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA), but unfortunately no T1-weighted scans were obtained before the administration of Gd-DTPA. It is thus uncertain whether the findings were, in fact, contrast enhancement, and therefore this patient was not included in the calculations. All contrast enhancements were found on MRI scans (7/39); no contrast enhancement was found on CT scans.

The prevalence of contrast enhancement among scans from long-term survivors of PML (patients who survived beyond 4 years from the date of PML diagnosis) was 18% (2/11 patients), and the prevalence of contrast enhancement on scans from PML progressors (patients who did not survive beyond 4 years from the date of PML diagnosis) was 14% (5/35 patients). Kaplan-Meier survival curves for patients with PML are shown in figure 1. A total of 39 patients with PML did not have contrast enhancement on CT or MRI scans, and 29 of these patients died during the study period. The median survival time in this group was 1.0 years (95% confidence interval [CI], 0–2.5 years). Of the 7 patients with PML who had contrast enhancement on CT or MRI scans, 5 died during the study period, with a median survival time of 1.6 years (95% CI, 0–4.9 years). In unadjusted Cox regression analyses, contrast enhancement on CT or MRI scans was not significantly associated with reduced mortality (mortality rate ratio, 0.88 [95% CI, 0.34–2.29]).

As Focosi indicates, opinions are not unanimous concerning the prognostic value of contrast enhancement on CT or MRI scans for patients with PML. In our study of HIV-infected patients with PML, the prevalence of contrast enhancement did not predict survival among long-term survivors, nor did it signifi-

Figure 1. Kaplan-Meier curves for overall survival among patients with contrast enhancement on computed tomography (CT) or magnetic resonance imaging (MRI) scans (dotted line) and among those without contrast enhancement on CT or MRI scans (solid line), by time after diagnosis of progressive multifocal leukoencephalopathy.