

phosphate homeostasis and vitamin D metabolism that are similar to those observed in oncogenic osteomalacia and X-linked hypophosphatemia. Because of these data from experiments *in vivo* and the finding that FGF-23 is readily detectable in plasma or serum from healthy persons, it appears likely that this protein has a pivotal role in phosphate homeostasis. However, the mechanisms through which phosphate homeostasis is affected by FGF-23 remain uncertain, particularly since studies exploring its effect on phosphate transport in opossum kidney cells and the effect of cleavage by PHEX have been conflicting.<sup>1-3</sup>

Our observation that about two thirds of the patients with X-linked hypophosphatemia in our study had increased levels of carboxy-terminal FGF-23 suggests new insights into the role of PHEX in the cleavage of intact FGF-23. Drs. Fukumoto and Yamashita point out that their FGF-23 assay, which presumably detects only intact FGF-23, yielded similar results.<sup>4</sup> If the data are confirmed in a larger series of patients with X-linked hypophosphatemia, the results could suggest that the two assays are of similar clinical utility. However, since the epitopes of the antibodies used in the assay of "intact" FGF-23 remain to be defined further, it is also conceivable that the two assays detect similar or identical, as yet undefined FGF-23 fragments that are normally cleaved by PHEX.

Exploring the regulation of phosphate homeostasis through FGF-23 remains challenging, and further work is required. Cell-based systems to assess the biologic activity of FGF-23 need to be im-

proved, PHEX-dependent cleavage of FGF-23 needs to be studied in more detail, and intact FGF-23 and its fragments (biologically active or inactive) need to be measured in patients with oncogenic osteomalacia, X-linked hypophosphatemia, and autosomal dominant hypophosphatemic rickets. The two available assays for FGF-23 will help in each of these important efforts. However, once FGF-23 cleavage by PHEX is better understood, it may well be necessary to develop additional assays that specifically detect the cleavage products as well as assays that detect the full-length substrate.

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## ZAP-70 in Chronic Lymphocytic Leukemia

**TO THE EDITOR:** Crespo et al. (May 1 issue)<sup>1</sup> present informative data on ZAP-70 as a surrogate prognostic marker for chronic lymphocytic leukemia (CLL). The patients in their study had heterogeneous backgrounds and may have been treated by different treatment strategies according to their age and disease status. Elderly patients with advanced or refractory CLL may have received less intensive treatment than others, leading to a poorer prognosis. Because treatments differ greatly in their effects on overall survival, there may have been a selection bias in the study. The authors have not provided sufficient information on these variables. Clinicians will appreciate it if the authors can share the data on treatments.

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**THE AUTHORS REPLY:** Murashige et al. make interesting comments concerning the clinical characteristics and treatment of the patients in our study. At our institution, patients in whom Binet stage A CLL is diagnosed do not receive therapy unless they

meet criteria for active CLL.<sup>1</sup> Treatment has, of course, varied over the years, from chlorambucil to fludarabine-based combination regimens. Interestingly, in our series, only 3 of the 18 patients with Binet stage A disease and low ZAP-70 expression required treatment, whereas 20 of the 26 patients with high ZAP-70 expression were treated. The main clinical variables, including age, did not differ between the two groups. Thus, with ZAP-70 analysis we were able to identify a group of patients with a bad prognosis, irrespective of the clinical stage. Finally, the relation among ZAP-70 expression, clinical variables, and survival should be assessed in larger series of patients.

The source of the monoclonal anti-ZAP-70 antibody used for flow cytometry was Upstate Biotechnology.

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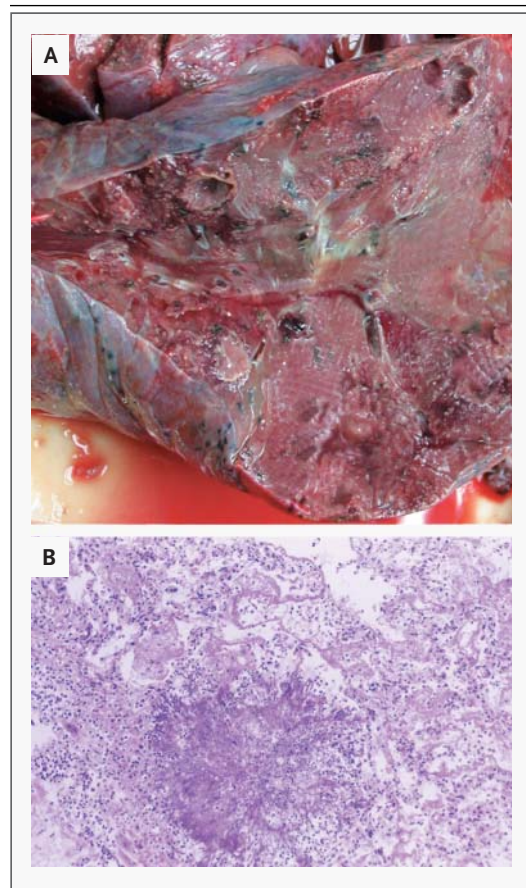
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## Fatal Aspergillosis in a Patient with SARS Who Was Treated with Corticosteroids

**TO THE EDITOR:** We report the case of a patient with severe acute respiratory syndrome (SARS) who died of aspergillosis after prolonged treatment with corticosteroids. The patient was a 39-year-old male physician based at the intensive-care unit of a small hospital in Guangzhou, China; he had no concurrent medical illness. Many patients with SARS were admitted to the hospital where he worked during the eight weeks before April 4, 2003, when he presented with a sore throat and a low-grade fever (37.3°C). Five days later, he had a high fever (38.5°C) and a low leukocyte count ( $3.4 \times 10^9$  per liter; 63.6 percent neutrophils and 26.2 percent lymphocytes), and he was admitted to the hospital with suspected SARS.

The patient was treated with twice-daily methylprednisolone (80 mg in the morning and 40 mg in the evening) for two days; the dose was decreased to 20 mg twice daily as the fever subsided, on April 12. The fever recurred on April 14, and chest radiography showed an infiltrate in the left lower lobe; the leukocyte count was  $13.5 \times 10^9$  per liter (94.0 percent neutrophils and 6.0 percent lymphocytes). Methylprednisolone was given again (20 mg in the morning and 80 mg in the evening), and the patient

was transferred to a larger hospital on April 15. Intravenous methylprednisolone therapy (80 mg twice daily) was then administered. The patient's



**Figure 1. Specimens of the Lung.**

Panel A shows the cut surface of a lung. The pathological specimen in Panel B shows extensive hyaline membranes, desquamated epithelial cells, and exuded monocytes in alveoli (hematoxylin and eosin,  $\times 100$ ). *Aspergillus* mycelia were observed on microscopical examination of the abscess and were isolated by culture as well.