AmB (0.1 mg every other day) was given through an Omaya reservoir (total dose, 1.2 mg), hyperbaric oxygen therapy was continued, and G-CSF therapy (5 μg/[kg·d]) was restarted.

Follow-up MRI on day 60 showed persistent abnormal enhancement of the left cavernous sinus and left frontal lobe, and biopsy of the left orbital fossa showed persistent nonseptated hyphae; culture was negative. As a result, the ABLC dosage was increased to 10 mg/[kg·d] for 2 months and then slowly tapered over 3 months. Total doses of 1.8 g of AmB and 60.3 g of ABLC were given in a 7-month period. A sharp increase in the creatinine level, from 1.8 mg/dL to 5 mg/dL (after 7 months of treatment), prompted cessation of therapy.

At the time of renal impairment, the patient also developed rash and fever concurrent with the use of a nonsteroidal antiinflammatory drug, a circumstance raising the question of whether the renal failure was a consequence of a hypersensitivity reaction rather than due to ABLC toxicity. G-CSF (5 mg/[kg·d]) was given for a total of 150 days. His average neutrophil count was 29,000/μL. The only adverse effect from G-CSF was occasional, mild bone pain.

Follow-up MRI at the end of therapy showed marked reduction in thickness of the left cavernous sinus and no evidence of inflammation involving the left frontal lobe. At follow-up 6 months after the end of therapy, the neurological examination findings were normal and the creatinine level was 1.6 mg/dL.

Lately, few case reports have suggested a beneficial role of G-CSF in the treatment of disseminated and rhinocerebral zygomycosis in immunocompromised patients [3, 4]. This patient was successfully treated with a combination of glycemic control, surgical resection of the involved facial tissue, and prolonged medical therapy. The administration of ABLC allowed us to use high doses of the medication for a long period and yet preserve renal function. The worsening renal function seen at the end of treatment might have been related to the high cumulative dose of ABLC or to the use of the nonsteroidal antiinflammatory drug, leading to a hypersensitivity reaction.

Six months after therapy was stopped, his renal function has improved remarkably. G-CSF was given at a dosage of 5 μg/[kg·d] in an attempt to improve the presumed abnormal neutrophil function. The only adverse effect seen with prolonged therapy was mild bone pain. The combined approach used to treat this patient suggests new strategies for this disease, which is generally associated with such a poor prognosis.

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References

Ritonavir, Triglycerides, and Pancreatitis

Protease inhibitors are recommended for the initial management of HIV infection [1]. The number of long-term studies evaluating the safety profile of this class of medications is limited, however. Herein we describe a patient with severe pancreatitis secondary to hypertriglyceridemia felt to be caused by the protease inhibitor ritonavir. Although previous studies have shown hypertriglyceridemia to be a side effect of ritonavir [2, 3], this particular complication has not been previously described. This case also suggests that these effects are not quickly reversed upon the discontinuation of ritonavir therapy.

A 46-year-old man was hospitalized for acute necrotizing pancreatitis. At presentation, laboratory values were as follows: serum lipase, 22,000 U/L; triglycerides, 67.31 mmol/L (5,957 mg/dL); and cholesterol, 24.02 mmol/L (929 mg/dL). Abdominal ultrasonography revealed a nondilated common bile duct. He did not consume alcohol. He had enjoyed good health until 2 years previously, when he was found to be HIV-positive. Before starting antiretroviral therapy, the cholesterol level was 4.24 mmol/L (165 mg/dL) and that of triglycerides was 1.33 mmol/L (118 mg/dL). For the preceding 2 months, his medications included ranitidine, alprazolam, ritonavir, saquinavir, zidovudine, lamivudine, and delavirdine. During the prior 18 months, he had taken saquinavir, zidovudine, and lamivudine without ill effects.

The level of triglycerides improved (2.82 mmol/L [250 mg/dL]) and the pancreatitis resolved following a prolonged fast. After 3 weeks of hospitalization, he was discharged to home; pancreatic enzymes, analgesics, and a low-fat diet were prescribed. He did not resume therapy with any antiretroviral agents.

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Two weeks later, he was seen in our lipid clinic. He was thin (weight, 63 kg) and muscle wasting was noted, but otherwise the examination findings were unremarkable. The CD4⁺ lymphocyte count was 517/mm³, and the viral load, as determined by HIV-RNA PCR, was 8,815 copies/mL. Blood glucose, hemoglobin Alc, thyroid-stimulating hormone, and serum amino-transferase levels were normal. The triglyceride level, however, had again risen to 25.24 mmol/L (2,234 mg/dL). The total cholesterol value was 7.26 mmol/L (281 mg/dL), and that of HDL cholesterol was 0.41 mmol/L (16 mg/dL). Gemfibrozil therapy was initiated. Antiretroviral therapy was re instituted with zidovudine, didanosine, delavirdine, nelfinavir, and saquinavir, and no complications were noted. Currently his cholesterol level is 4.91 mmol/L (190 mg/dL), and the triglyceride level is 4.79 mmol/L (424 mg/dL).

Markowitz et al. [3] demonstrated triglyceride level elevations in excess of 200% over baseline values in 65% of patients receiving ritonavir. These effects on serum lipids appear to be dose-related and can be seen as early as 1 week after initiation of therapy with ritonavir [2].

The mechanisms leading to hyperlipidemia with ritonavir are not known. Although ritonavir inhibits the CYP3A4 isoform of cytochrome P450 [4], there is no definitive evidence that inhibition of this enzyme leads to hyperlipidemia [5]. Recently, it has been suggested that protease inhibitors may alter the structure or function of the peroxisome proliferator-activated receptor type gamma (PPAR-gamma), but this has yet to be studied fully [6].

HIV infection alone is associated with hypertriglyceridemia, and the triglyceride level correlates inversely with the CD4⁺ lymphocyte count [7]. The degree of hypertriglyceridemia attributed to HIV infection, however, is generally less than that described in this case [8]. Furthermore, triglyceride levels tend to be normal in HIV-infected individuals who have no manifestations of AIDS [9].

Clinicians need to be familiar with the association between ritonavir and hyperlipidemia, and serum lipids should be monitored during the early stages of ritonavir treatment or with escalation of the dose. It is not yet known if use of ritonavir is safe for patients with abnormal lipid values at baseline; however, further investigation is warranted.

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References

Myocardial Infarction, Culture-Negative Endocarditis, and Chlamydia pneumoniae Infection: A Dilemma?

The role of Chlamydia pneumoniae infection in cardiovascular diseases remains unclear. Herein we describe a case in which the many aspects of possible involvement are illustrated.

A 67-year-old woman previously in good health was admitted for pulmonary edema. An electrocardiogram showed typical signs of acute myocardial infarction. Echocardiography revealed severe aortic-valve regurgitation, moderate mitral-valve regurgitation, and a vegetation (5 × 14 mm) on the right coronary leaflet of the aortic valve. There was no history of fever, weight loss, or shaking chills in the preceding weeks.

The axillary temperature was 36.2°C, pulse was 110/min, and blood pressure was 120/70 mm Hg. A 3/6 holosystolic murmur and a 2/6 diastolic decrescendo murmur were noted. Skin and mucous membranes as well as funduscopic findings were normal.

The C-reactive protein level was 114 mg/L. The leukocyte count was 13,400/mm³, with a normal differential, and the serum chemistry was compatible with recent myocardial infarction. Three pairs of aerobic and anaerobic cultures of blood drawn before administration of antibiotics remained negative. Antibiotic therapy with high-dose intravenous fluvoxacinil, later replaced by penicillin and gentamicin, was initiated. Body temperature was <37°C, except for two spikes to 38.4°C on days 14 and 16. Doxycycline and rifampicin were added on day 14.