Treatment with Deferoxamine: A Real Risk Factor for Mucormycosis?

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Dear Sir,

Treatment with deferoxamine in patients with iron-overload or in dialysis patients with aluminum overload is increasingly recognized as a risk factor for the development of infections caused by *Yersinia enterocolitica* and *Rhizopus oryzae* [1–5]. *Y. enterocolitica* is unable to produce its own iron-binding molecules and utilizes siderophores produced by other microorganisms [1]. Deferoxamine, a siderophore produced by *Streptomyces pilosus*, may inhibit growth of most bacterial strains by binding the iron that is needed for bacterial multiplication [6]. On the other hand, deferoxamine may stimulate the growth of microorganisms like *Y. enterocolitica* by acting as a carrier for iron [7]. This phenomenon may explain the increased risk for infections with *Y. enterocolitica* in patients treated with deferoxamine. Based on clinical observations, the same pathogenic mechanism is assumed for infections caused by *R. oryzae* [2–4]. In addition to the reported cases of mucormycosis in patients treated with deferoxamine, the following patient is presented.

Recently, a 55-year-old man with sideroblastic anemia, was treated with deferoxamine for secondary iron overload (serum ferritin 3618 ng/l) after multiple blood transfusions. There were no signs of organ dysfunction due to iron toxicity and the patient was not diabetic. He was receiving the drug intramuscularly at a dose of 500 mg/day for 5 days. One week after the start of this treatment a right-sided orbital cellulitis with an ethmoiditis developed. A punctate of the ethmoid yielded growth of *R. oryzae*. Despite intravenous amphotericin B which was administered to a total dose of 875 mg in the subsequent 35 days, blindness of the right eye developed due to occlusion of the central retinal vessels. The neurological condition of the patient deteriorated as the result of an ischemic infarction of the right-sided basal ganglia, Table 1. Effect of deferoxamine on growth of *R. oryzae*

A constant spore inoculum quantity ($1,000 \times$ dilution of absorbance 0.1 at 660 nm) was incubated at 37°C in 10-μl cups cut out in 20 ml 2% dextrose agar (pH 5.6). Growth was determined by measuring the radius of the zone of exhibition around the cup. Iron-saturated deferoxamine and EDTA were prepared by adding FeCl₃ to chelator brought to pH 2. The pH was then slowly adjusted to 7.4. Numbers are mean ± SD of three experiments in duplicate.

as could be demonstrated by CT scanning. At autopsy, ischemic necrosis of the basal ganglia was confirmed. Unfortunately, the cerebral blood vessels and the orbital content were not thoroughly examined and *R. oryzae* was not demonstrated.

To answer the question whether a relationship could exist between mucormycosis and the deferoxamine treatment in this iron-overloaded patient, we investigated in vitro the effect of iron and deferoxamine on the growth of the *R. oryzae*, which was obtained from the ethmoid during life. The fungus was cultured in media with iron bound to citrate, deferoxamine, and iron-saturated deferoxamine. As can be seen in table 1, no significant difference in growth was noticed. Interestingly, when ethylene-diaminetetraacetic acid (EDTA) was added to the culture

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medium, growth of *R. oryzae* was completely inhibited. 3 Saturation with iron abolished the inhibiting effect of EDTA and the calcium chelator ethyleneglycoltetraacetic acid (EGTA) did not influence fungal growth (data not shown). These data suggest that the growth-inhibiting effect of EDTA is the result of depletion of iron that would otherwise have been used for fungal multiplication. 6

Because in recent years mucormycosis has mainly been reported in patients treated with deferoxamine, a causative role for deferoxamine is suggested. However, 7 in contrast to *Y. enterocolitica*, *R. oryzae* does excrete siderophores [8] and our laboratory data indicate that addition of deferoxamine to the culture medium does not increase the growth of *R. oryzae*. We agree with Boelaert et al. [9] that more data are needed to determine whether 9 treatment with deferoxamine for iron or aluminum overload is really a risk factor for mucormycosis.

References