A Common Mold, An Uncommon Killer

Jonathan Reisman, MD

A sixty year-old man comes into the intensive care unit gravely ill, with respiratory and circulatory systems failing. He is intubated, put on a ventilator, and medications are infused intravenously to restore his blood pressure ensuring oxygen delivery to his brain and other vital organs. He is stabilized.

A sample of his sputum, secretions from deep inside the lung, is sent to the microbiology lab for testing. A technician smears the sputum onto a glass slide and dribbles on a few drops of potassium hydroxide solution. She looks under the microscope and sees fungal hyphae with conspicuous septations. She spreads the sputum on agar to grow a culture of potential pathogens that may be infecting the patient's lungs.

Over the next few days the patient's clinical status worsens. The agar culture of his sputum grows out multiple colonies of *Aspergillus fumigatus*. His lungs are infected, and he is failing despite maximal medical therapy. Further treatment is deemed futile. Medical care is withdrawn and he quickly passes away.

Aspergillus fumigatus is a ubiquitous mold found virtually everywhere, and it plays a fundamental role in the degradation of organic matter on earth. It can be found on plants, dirt, and dust; in kitchens, bathrooms and basements; and even inside used pillows (Woodcock et al., 2006). Everyone lives their entire life in intimate association with *A. fumigatus*, inhaling its spores with every breath, yet the kind of invasive lung infection seen in this patient is rare. So why, then, does this pervasive, and usually harmless, organism sometimes become a killer?

The answer is in the human immune system and its ancient familiarity with

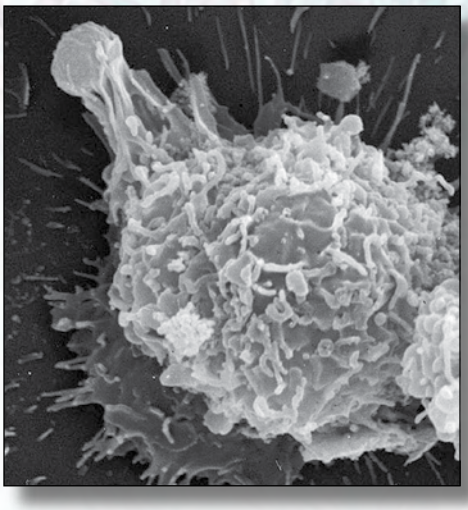


Figure 1 (above). Scanning electron micrograph of a mouse macrophage reaching with pseudopodia to grab and ingest a conidium of *Aspergillus fumigatus*. Courtesy of Dr. O. Ibrahim-Granet, Institut Pasteur, France; see Ibrahim-Granet et. al., 2003.

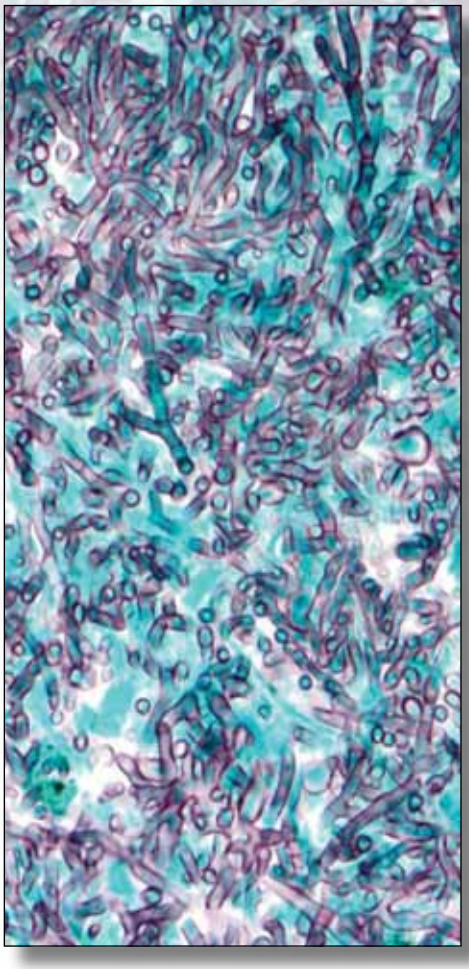
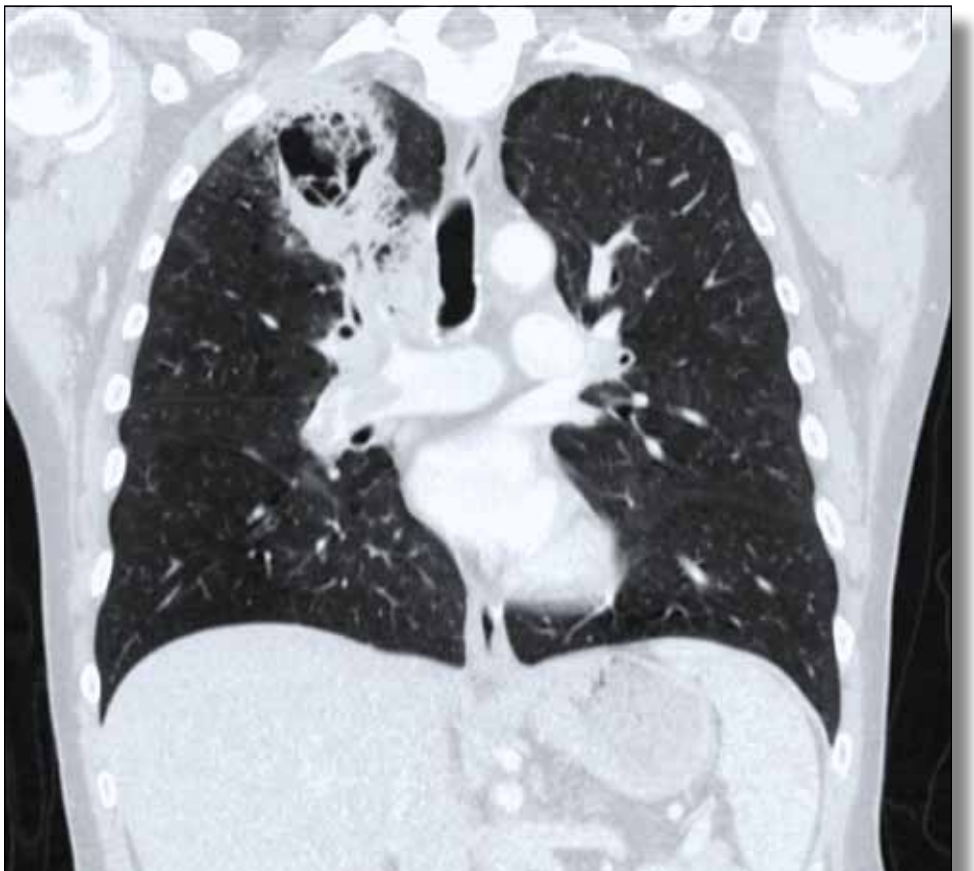


Figure 2 (above). A methenamine silver stain of *Aspergillus fumigatus* seen through a light microscope. Courtesy Dr. Eugene Mark.

Figure 3 (below). The cavitary lesion seen in the upper lobe of the lung on this CT scan was caused by infection with *Aspergillus fumigatus*.



this mold. In health, the immune system is a finely orchestrated, multi-tiered defense system that is constantly at work fending off microbes of everyday life such as *A. fumigatus.* Having evolved in the constant presence of this ancient acquaintance of humanity, the immune system is exquisitely designed to fend it off. With each breath conidia land in the lung's deepest pockets, the alveoli, and are killed by well-trained white blood cells called *macrophages*, or "big eaters" (Figure 1). Once inside a macrophage, conidia are killed by a burst of hydrogen peroxide and other caustic substances—a chemical weapon called the "oxidative burst" that serves as the primary killing tool of the immune system's foot soldiers.

The macrophages represent just one aspect of a very complex defense system, and if any aspect of the system is deficient, if there is any chink in the armor, a normally harmless mold like *A. fumigatus* can become a killer. This is exactly what happened with our unfortunate patient—his macrophages were unable to muster the oxidative burst needed to kill this invading fungus. And the reason for his immunodeficiency goes back to the very first step in any immune response: recognition of the enemy.

Before killing a conidium, macrophages must first recognize it as something foreign and, importantly, differentiate it from the body's own tissues which must be protected like innocent bystanders. The ability of the immune system to recognize an invading microbe can be acquired, such as by getting an infection or receiving a vaccine which primes the recognition software to be ready the next time that that microbe appears. But white blood cells also have an innate ability to recognize invaders—an ability that is passed down through genes and does not require an initial exposure to be prepared. This innate ability is partly due to proteins called "toll-like receptors" (TLR's) which are designed to recognize specific types of carbohydrate or protein patterns found specifically in microbes but not in human cells. Several of these proteins, which are programmed by genes found in every human, specifically recognize patterns found in the cell wall of *A. fumigatus* and nowhere else in nature.

So it turns out our macrophages have an intimate and ancient familiarity with *A. fumigatus* before a newborn baby even takes the first moldy breath. And this fine-tuned adaptation is what facilitates a healthy respiratory life despite the daily load of this mold entering the lungs. Unlike our brains which must learn to differentiate poisonous from edible fungi, our immune systems can recognize some fungi from birth.

Our patient's immune system initially suffered from faulty recognition, specifically in telling apart the enemy from the self. Three weeks before being infected by *A. fumigatus*, he had been diagnosed with an "auto-immune hemolytic anemia." In auto-immune disease, the immune system mistakes the body's own tissues for an enemy and attacks it. In his specific condition the immune system was destroying his own red blood cells, called a "hemolytic anemia." Glucocorticoids, or "steroids," are a mainstay of treatment for all auto-immune conditions, and they work by shutting down the immune response that is attacking the self. Unfortunately they are non-specific in their effects on the immune system, and they also shut down the macrophages prowling through the alveoli. Studies in mice show that steroids do not alter the recognition or engulfment of *A. fumigatus* conidia by macrophages, however they weaken considerably the white blood cell's ability to produce the oxidative burst that would kill this mold (Philippe et al. 2003). Once engulfed by a macrophage on steroids, *A. fumigatus* conidia can germinate and send hyphae through and out of the macrophage killing it and invading the lung. Steroids made this patient "immunocompromised," and that is how a ubiquitous mold became his killer.

Even with appropriate treatment invasive infections with *A. fumigatus* have a very high mortality rate. In the last several decades the number of such infections in the U.S. has increased dramatically—not because the mold is becoming more prevalent (it has always been omnipresent), but because there are more people around with compromised immune systems. Patients with cancer, organ transplants, HIV/AIDS, auto-immune disease, and congenital

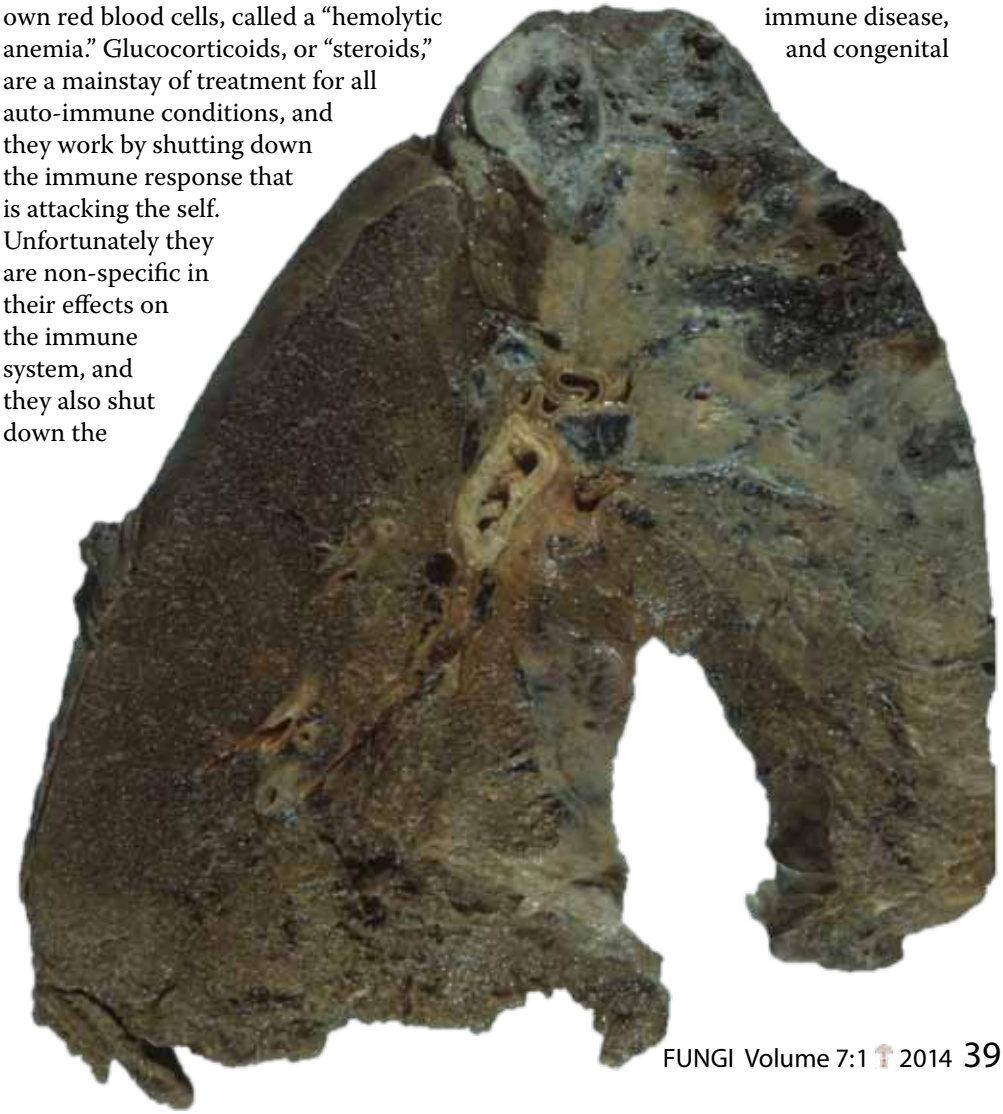


Figure 4. A similar cavitary lesion in the lung caused by *Aspergillus fumigatus* shown in a pathology specimen.

immunodeficiencies are surviving longer than ever before thanks to advances in medicine. Such people with dysfunctional immune systems are something of a new species on earth, one that could never have survived in past eras due to culling by *A. fumigatus* and other microbes of everyday life. Despite medical advances, though, these patients remain in danger of contracting infections with these microbes. Life on earth demands living in harmony with *A. fumigatus*, and this is not possible with an under-functioning immune system.

But the opposite is also true—an immune system that *over*reacts to *A. fumigatus* can also cause harm, such as in allergic disease. While auto-immune disease is a mistaken immune system that has recognized a friend for an enemy, allergic disease is correct recognition but a gross overreaction to an enemy. With allergies such as hay fever or asthma, the immune system fights too strongly against an invader that would otherwise not cause much trouble, and ends up injuring the self as collateral damage. *Aspergillus fumigatus* is one common target of these overreactions. In patients overly sensitized to this mold, doctors recommend reducing exposure to moist basements, carpets, and old pillows: places where *A. fumigatus* thrives.

Ultimately the trick to living in harmony with *A. fumigatus* is to be able to fend off this fungus without overacting to it. The human body has to walk a fine balance between under- and over-reacting, or else life in this fungal blizzard called the earth's atmosphere would be impossible. TLRs and other new discoveries of human biology show just how exquisite this balance is, and how truly profound is our relationship with this microbe.

References

Ibrahim-Granet, O., B. Philippe, H. Boleti, E. Boisvieux-Ulrich, D. Grenet, M. Stern and J. P. Latgé. 2003. Macrophages *Aspergillus fumigatus* conidia in alveolar phagocytosis. *Infection and Immunity* 71(2): 891.

Philippe, B., O. Ibrahim-Granet, M.C. Prévost, M.A. Gougerot-Pocidalo, M. Sanchez Perez, A. Van der Meeren, and J.P. Latgé. 2003. Killing of *Aspergillus fumigatus* by alveolar macrophages is mediated by reactive oxidant intermediates. *Infection and Immunity* 71(6): 3034-3042.

Woodcock, A.A., N. Steel, C.B. Moore, S.J. Howard, A. Custovic, and D.W. Denning. 2006. Fungal contamination of bedding. *Allergy* 61: 140–142.