Invasive aspergillosis in a patient with MELAS syndrome

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Abstract

Invasive infection with the opportunistic fungus Aspergillus fumigatus predominantly affects people with impaired cell mediated immunity. The case of a 31 year old woman with no identified cause for immunosuppression who presented with severe refractory aspergillosis of the paranasal sinuses is reported. She subsequently developed clinical and molecular evidence of mitochondrial encephalomyopathy with lactic acidosis and stroke-like events (MELAS) syndrome. It is proposed that MELAS syndrome may represent an unusual risk factor for the development of invasive aspergillosis and mechanisms are supported by which mitochondrial dysfunction may predispose to this.

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Aspergillus fumigatus is an opportunistic infection which usually affects the lungs, sinuses, or the tracheobronchial tree. Risk factors for the development of invasive aspergillosis include severe inherited abnormalities of granulocyte function such as chronic granulomatous disease and severe combined immunodeficiency syndrome, cytotoxic chemotherapy for malignancies such as leukaemia and lymphoma, AIDS, and iatrogenic immunosuppression in transplant recipients.1 The risk of developing invasive aspergillosis in the normal healthy and fully immunocompetent host is negligible, although a few such cases have been described.1 2

The syndrome known as mitochondrial encephalomyopathy with lactic acidosis and stroke-like events (MELAS) is one of a group of disorders known to be caused by mutations in mitochondrial DNA. The cardinal features of the disorder are stroke-like episodes before the age of 40, encephalopathy characterised by seizures, dementia, or both, and lactic acidosis or ragged red fibres on muscle biopsy.3

In addition to the cardinal features of the disease, many other manifestations have been described including sensorineural deafness, diabetes mellitus, cardiac conduction abnormalities, and intestinal pseudo-obstruction.4 No previous association between MELAS syndrome and opportunistic infection has been reported.

Case report

A previously fit and well 34 year old woman presented in 1991 complaining of blockage of the right nostril associated with bloody discharge. On examination there was gross deviation of the nasal septum and some crusting around the right nostril. Cranial CT showed extensive mucosal change with a soft tissue mass in the right nasal cavity and maxillary antrum, extending into the right ethmoid and sphenoid sinuses and with associated bony destruction of the medial wall of the right orbit. A submucosal resection was performed and disclosed large amounts of thickened green necrotic material. A biopsy subsequently grew Aspergillus fumigatus. Despite two extensive internal debridements the disease progressed. External ethmoidectomy was performed and further histology confirmed continuing invasion of the mucosa by hyphae, with no evidence of a host reaction to the infection.

Further treatment with itraconazole failed despite high doses, and treatment with amphotericin B, both deoxycholate and lipid associated (Amphocil), resulted in a partial response. Despite two extensive nasal debridements the disease progressed. On June 12, 2001 by guest. Protected by copyright.
Aspergillus accumulation and insulin resistance in both excess toxic free radical enzymes of the inner mitochondrial membrane that dysfunction of the respiratory chain dated; however, there is evidence to suggest the mechanism of cellular damage is not fully elucidated. Neutrophils and other phagocytes form a crucial part of the defence against fungi such as Aspergillus. Effective function of neutrophils depends on a series of steps conventionally divided into stimulus detection and transduction, chemotaxis, ingestion, degranulation, and microbial killing.

After stimulus detection the neutrophil must move actively by diapedesis to the site of inflammation. The mechanism of the movement involves, as in muscle cells, the interaction of actin and myosin and the consumption of ATP as an energy source for this active process. Defects in the mitochondrial respiratory chain enzymes may render the neutrophil unable to produce the energy necessary to perform effective chemotaxis. Degranulation of neutrophils similarly requires active movement of actin on myosin and is an energy dependent process indirectly relying on mitochondrial function. Neutrophilic microbial killing is effected by several mechanisms, but the most important of these is an oxygen dependent killing system termed the “respiratory burst of phagocytosis”. This comprises a rapid set of metabolic events which begin with the reduction of molecular oxygen to superoxide, a free radical anion, by the multicomponent enzyme system NADPH oxidase.

Superoxide free radicals proceed to form hydrogen peroxide and other more potent reactive oxygen species which are toxic to ingested microorganisms and effect microbial killing, along with significant damage to the neutrophils themselves. Although the NADPH oxidase enzyme system is not mitochondrial in location, the generation of NADPH and its maintainance in a reduced state requires functional respiratory chain enzymes.

Defects in the NADPH oxidase enzyme system are known to produce various forms of chronic granulomatous disease, which characteristically result in impaired immunity to bacterial and fungal infections, particularly Aspergillus. An unusual feature of neutrophilic killing of Aspergillus is that, unlike other microorganisms, the fungus is not ingested but rather killed extracellularly.

It is well known that acidic, lactate based peritonial dialysis solutions have a detrimental effect on neutrophil function, and that the longer the exposure to one of these solutions the worse is the ability of neutrophils to form superoxide anions which are necessary for the effective killing of many microorganisms including Aspergillus. Perhaps the most important potential mechanism of neutrophil dysfunction in the patient described is the likelihood of longstanding lactic acidosis, which in MELAS syndrome is often accompanied by episodes of more severe acidosis coinciding with intercurrent infection.

It is interesting to note that despite these potential causes for impaired neutrophil function in MELAS syndrome, the patient underwent full immunological investigation at the beginning of her disease and no abnormalities were discovered. This may be because standard neutrophil function testing involves measurement of phagocytosis of Candida; however, this is a relatively crude assay and only major defects would be elicited by these tests. Furthermore, no measure of extracellular killing is obtained. It is thus possible to have immune defects which result in significant reduction in defence against Aspergillus with normal laboratory testing of Candida phagocytosis and killing. In addition, in vitro testing under buffered conditions may not elucidate problems related to in vivo lactic acidosis, which is likely to be a significant factor in the patient described.
A further possible discrepancy could arise because of the phenomenon of heteroplasmy which is found in mitochondrial disorders. In genetic disorders affecting the nuclear DNA, the mutations are expected to be equally distributed in cells throughout the body. In mitochondrial DNA mutations, heteroplasmy ensures random distribution of the abnormal mitochondria and the numbers of mitochondria affected may vary dramatically in different cells and tissues. It is possible that by chance the neutrophils assayed in vitro had a low proportion of mutant mitochondrial DNA, and if outnumbered in vivo by cells with a high mutant load this could cause a significant degree of immunosuppression by the mechanisms postulated above.

This is the first reported case of invasive aspergillosis in a patient with a mitochondrial disorder. Although the mechanism is unknown, mitochondrial disorders may represent an unusual risk factor for the development of this infection, and further studies are needed to assess the effects of mitochondrial dysfunction on the immune system. MELAS syndrome and other mitochondrial defects should be excluded in patients with invasive aspergillosis not apparently immunocompromised.