Netherlands
The Journal of Medicine

REVIEW

Immunoparalysis in sepsis

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ABSTRACT

Although therapeutic opportunities in medicine continuously improve, death is inevitable in some cases due to limitations in treatment. When patients die without a conclusive diagnosis, autopsy studies can provide essential information in order to improve pathophysiological reasoning. We describe two patients who died after a prolonged course of sepsis and were diagnosed with the unsuspected presence of aspergillosis at autopsy. Literature review demonstrates that due to apoptosis and immunological interactions, septic patients become susceptible to opportunistic infections, a state described as immunoparalysis.

KEYWORDS

Aspergillosis, immunosuppression, sepsis, T cell differentiation

What was known about this topic?
Implementation of the Surviving Sepsis Guidelines has led to optimisation of patient care during the hyper-inflammatory phase of sepsis. Mortality in these patients, however, remains relatively high. Invasive aspergillosis is a severe fungal infection that affects immunocompromised patients, but is also described in intensive care patients with no prior history of immunosuppression.

What does this add?
These two cases demonstrate that a prolonged state of sepsis impairs cellular immune system functioning and predisposes patients to opportunistic infections. Disseminated invasive aspergillosis can develop without clinical suspicion and could be the cause of persistent multi-organ dysfunction syndrome. The immunological disturbances that have been described in recent studies may provide potential improvements in the therapeutic strategy for sepsis, but source control will remain a big issue.

INTRODUCTION

Sepsis embodies a cascade of systemic inflammatory responses that may progress to severe sepsis and septic shock. It is one of the leading causes of in-hospital death worldwide and represents 11-20% of all intensive care admissions.[1,2] Mortality increases with severity, and is approximately 46% for patients in septic shock.[3] In the Netherlands, sepsis represents approximately 3500 deaths annually.

The Surviving Sepsis Campaign has developed a resuscitation and management bundle in order to standardise patient care in the initial hours after admission.[4] National and international studies have demonstrated that implementation of these bundles significantly reduces mortality.[2,5,6] However, even when optimal support is provided, mortality remains relatively high.

CASE REPORTS

A 67-year-old patient with a medical history of chronic obstructive pulmonary disease and paroxysmal atrial fibrillation presented to the emergency department with complaints of melaena. Gastroscopy revealed an intramucosal adenocarcinoma of the pyloric antrum, for which he underwent subtotal gastric resection. The postoperative course was complicated with persistent fever and haemodynamic instability. Imaging studies revealed anastomotic leakage, for which surgical reconstruction was performed. Blood cultures were positive for *Streptococcus milleri, Candida albicans* and *Enterococcus faecium* successively. Although sputum cultures once showed

growth of *Aspergillus species*, Galactomannan enzyme immunoassay was not performed. The patient's condition did not improve and leakage of pancreatic secretion caused recurrent gastrointestinal blood loss. CT scan of the thorax revealed atelectasis of the left lower lobe with mild pleural effusion and persistent abdominal fluid collections. Despite repetitive surgical interventions and extensive antibiotic and antifungal treatment, the patient remained septic and eventually died due to multiple organ dysfunction. Autopsy revealed the unsuspected presence of aspergilloma in the respiratory tract with systemic activity and metastatic growth in the heart and kidneys (*figure 1*).

Two years earlier, a 52-year-old patient with no relevant medical history had developed a similar course after surgical resection of a perforated ileum. Postoperatively, she remained dependent on ventilatory and haemodynamic support. Multiple surgical interventions were performed in order to correct anastomotic leakage, but septic shock persisted. Blood cultures revealed sequential growth of *Pseudomonas aeruginosa, Enterococcus faecium* and *Candida albicans*. Thoracic CT scan showed ground glass opacity in the basal fields bilaterally and cystic bronchiectasis in the right lower lobe. As in the case above, *Aspergillus fumigates* was grown once in the sputum but Galactomannan enzyme immunoassay was not performed. Eventually, the patient developed a severe encephalopathy and although extensive antibiotic treatment was administered, she remained in a depressed state of consciousness. CT cerebrum suggested haemorrhagic lesions in the frontal lobe (*figure 2*). Consecutive electroencephalography did not reveal improvement in cerebral performance and therefore multidisciplinary consultation concluded to discontinue supportive treatment. At autopsy, vaso-invasive growth of *Aspergillus* was found bilaterally in the lungs, with systemic mycotic emboli and metastatic involvement of the cerebrum.

Figure 1. *Growth of Aspergillus in the myocardium*

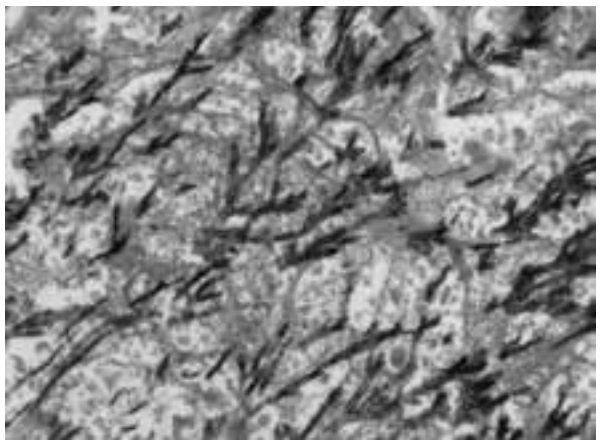
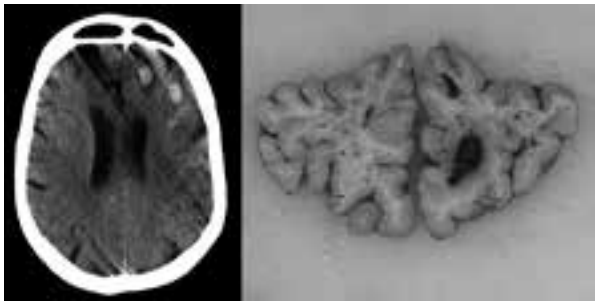


Figure 2. *Cerebral lesions on CT scan were classified as metastates of invasive aspergillosis at autopsy*

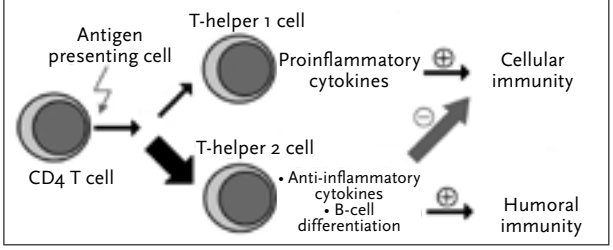


DISCUSSION

As these two cases evidently demonstrate, opportunistic infections may develop in critically ill patients with no history of immune suppression. Invasive aspergillosis is a life-threatening infection that primarily affects patients with haematological malignancies, autoimmune diseases, AIDS or immunosuppressive therapy. Diagnosis is difficult to obtain, since it requires presence of *Aspergillus* in the histopathological analysis of sterile tissue specimens. In the last decade, several case series have described invasive aspergillosis in intensive care patients without a history of immune suppression.[7,8] It seems multi-organ dysfunction syndrome predisposes patients to opportunistic infections. In 1995, Ertel *et al*. demonstrated that the release of pro-inflammatory cytokines in whole blood was significantly impaired in septic patients compared with control patients without infection.[9] Autopsy studies later revealed profound apoptosis of B cells, CD4 T cells and follicular dendritic cells in patients who died of sepsis.[10] The apoptosis of these cells appears to play a key role in the pathophysiology of immune suppression.

A decrease in the absolute number of circulating lymphocytes and dendritic cells obviously reduces the functioning of the immune system. Furthermore, presence of apoptotic lymphocytes substantially increases anti-inflammatory cytokine production and impairs the release of pro-inflammatory cytokines (IL-10 and TNF-α respectively).[11] The production of these cytokines is directed by CD4 T cells, which are activated by antigen-presenting cells and can either proliferate to T-helper 1 or T-helper 2 cells. The presence of T-helper 1 cells stimulates cytotoxic T cells and thereby increases cellular immunity, whereas T-helper 2 cells stimulate humoral immunity and simultaneously provide negative feedback to the cellular immune system. After ingestion of apoptotic cells, antigen-presenting cells predominantly stimulate the proliferation of CD4 T cells in T-helper 2 cells and cause an overshoot in negative feedback to cellular immunity (*figure 3*).[10,12]

Figure 3. *Presence of apoptotic cells stimulates proliferation of CD4 T cells into T-helper 2 cells and thereby causes an overshoot in negative feedback to cellular immunity*



Since the cellular immune system is crucial for protection against opportunistic infections, patients become less competent in eliminating these opportunists. Lastly, the presence of apoptotic cells seems to accelerate lymphocyte tolerance to pathogens, a mechanism described as anergy.[12] The combination of these pathways causes cellular immune system paralysis.

In conclusion, the cascade of sepsis does not end at the stage of septic shock. Immune responses in sepsis are biphasic; the initial hyper-inflammatory phase is followed by anti-inflammatory reactions that induce immunoparalysis. During sepsis, patients with prior normal immune system functioning become susceptible to opportunistic infections such as invasive aspergillosis. This may partially explain the mortality that persists despite the implementation of the Surviving Sepsis Guidelines. Further insight into the immunological disturbances in septic patients may lead to the development of immunomodulatory therapy. Currently, several potentially beneficial immunosupportive agents are being studied in clinical trials.[13,14]

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