Eur J Clin Microbiol Infect Dis (2005) 24: 628–633
DOI 10.1007/s10096-005-0006-x

CONCISE ARTICLE

H. Sambatakou · D. W. Denning

Invasive pulmonary aspergillosis transformed into fatal mucous impaction by immune reconstitution in an AIDS patient

Published online: 22 September 2005

Abstract Reported here is the case of a newly diagnosed AIDS patient with end-stage HIV infection and biopsy-proven invasive pulmonary aspergillosis who responded to antifungal therapy but developed severe mucous impaction in association with rapid immune restoration that was ultimately fatal. Invasive pulmonary aspergillosis complicates about 4% of AIDS infections. A search of the medical literature revealed no previous report of this organism's involvement in immune restoration syndrome.

Introduction

Highly active antiretroviral therapy (HAART) has had a profound biological impact on the clinical manifestations of HIV infection. It has dramatically decreased the frequency of opportunistic infections (OIs), which had been the hallmark of HIV infection, independent of the use of specific OI prophylaxis. This appears to result from the partial recovery of the host's immune system, characterized by a profound and sustained suppression of viral replication and a variable increase of the CD4+ cell count in blood, with significant rises in the numbers of CD4+ cells of both naïve and memory phenotype. An additional remarkable effect of antiretroviral therapy (ART) has been the resolution of certain complications for which no effective therapy was available previously, such as progressive multifocal leukoencephalopathy, cryptosporidiosis, microsporidiosis, azole-resistant candida esophagitis, molluscum contagiosum, and Kaposi's sarcoma.

Despite the marked improvement in patient survival and reduction in the incidence of HIV-related OIs following the introduction of HAART, these infections remain a challenge in the management of HIV-infected patients. Since the introduction of HAART in 1996, new clinical observations of florid inflammatory responses to infectious agents have been noted, which have come to be known as immune reconstitution syndrome (IRS). This exacerbation of a wide variety of latent infections, with the expression of complex clinical pictures and paradoxical reactions, coincides with improvements in CD4+ lymphocyte counts and decreases in plasma viral load and is probably related to an antigen-specific T-cell response. In contrast to clinical manifestations of OI during immunosuppression, which are characterized by a high microbial tissue burden and systemic dissemination, the manifestations of IRS are characterized by a local reaction with sparse isolation of the complicating pathogen. Examples are focal *Mycobacterium avium* infection without positive culture, cryptococcal meningitis with marked cerebrospinal fluid pleocytosis, *Pneumocystis carinii* pneumonia (PCP), mild herpes zoster virus infection, progressive multifocal leukoencephalopathy with contrast enhancement, cytomegalovirus (CMV) vitreitis, and paradoxical expansion of local tuberculosis lesions with sparse acid-fast bacilli [1, 2].

Apart from infections, IRS also includes exacerbation of AIDS-associated malignancies, such as Epstein Barr virus-related lymphoma, Kaposi's sarcoma and human papilloma virus-related anogenital squamous cell cancer, and other noninfectious disorders, such as worsening of Grave's disease, autoimmune thyroiditis, systemic lupus erythematosus, Castleman disease, Guillain-Barré syndrome, pulmonary sarcoidosis and sarcoid-like disorders [3–6]. Until now, aspergillosis has not been included in IRS. We describe here the remarkable shift in the clinical picture of an HIV-infected patient during rapid immune reconstitution in what is believed to be the first case of IRS associated with aspergillosis.

H. Sambatakou · D. W. Denning
Education and Research Centre,
Wythenshawe University Hospital,
Southmoor Road,
Manchester, M23 9LT, UK

H. Sambatakou (✉)
Infectious Diseases Unit,
General Hospital "G. Gennimatas",
154 Messogeion Avenue,
11527 Athens, Greece
e-mail: helen2@otenet.gr
Tel.: +30-210-7489252
Fax: +30-210-7788110

Case report

A 58-year-old homosexual man was newly diagnosed as HIV positive following an 8-month history of weight loss, night sweats and recent dysphagia due to herpes simplex virus esophagitis. At the time of diagnosis he was mildly pancytopenic with abnormal liver function test results and hypoalbuminemia, while his baseline chest radiograph was normal. The laboratory test results were as follows: hemoglobin, 11.5 g/dl; leukocyte count, 3.2×10^9 cells/l (lymphocytes 0.97×10^9/l, neutrophils 1.84×10^9/l, eosin 0.03×10^9/l); platelets, $81{,}000\times10^9$/l; creatinine, 48 mmol/l; urea, 8.7 mmol/l; total protein, 50 g/l; albumin, 16 g/l; total bilirubin, 13 mmol/l; alkaline phosphatase, 325 IU/l; alanine transferase, 59 U/l; gamma glutamyltransferase, 228 IU/l; VDRL negative; toxoplasma immunoglobulin (Ig)G antibodies, <1/32; hepatitis B surface antigen, hepatitis B core antibody and hepatitis C virus antibody negative; CD4+ cell count, 5/μl; CD8+ cell count, 84/μl; and viral load, $>10^6$ copies/ml.

After a few days of total parenteral nutrition, PCP was diagnosed presumptively. A chest radiograph performed at that time showed increased pneumonic shadowing within both lungs, principally on the right side, with a reticular interstitial pattern and some alveolar shadowing, which was consistent with the current diagnosis. The patient responded to cotrimoxazole therapy with adjuvant prednisolone (40 mg b.i.d. daily for 5 days then 20 mg q.i.d. daily). Emergency bronchoscopy did not reveal any endobronchial lesions and cultures of bronchoalveolar lavage were negative for acid-fast bacilli and mycobacterial, viral and fungal infection. Another chest radiograph performed 2 weeks following the commencement of anti-PCP treatment showed a new round shadow in the right upper zone, with impression of cavitation. However, the patient was afebrile with no chest symptoms at that time and his blood gases on air had improved. PCP treatment was discontinued after 28 days, but secondary prophylaxis was maintained. Bone marrow examination showed normal architecture and cellularity with progressively increasing peripheral platelets.

A new chest radiograph performed 4 weeks after the second radiograph revealed bilateral anterior cavitating lesions in the upper lobe, and the pre-existing signs on the right had increased in comparison with the previous image (Fig. 1). However, the patient remained afebrile and asymptomatic, he was gaining weight, and only a few crackles were present on physical exam. The above findings were confirmed by computed tomography scan, which showed bilateral heterogenous areas of increased attenuation in the upper zone with evidence of cavitation anteriorly adjacent to the chest wall and surrounding fibrotic change. A lung biopsy of the anteriorly situated left apical cavity was performed, which showed necrotic lung colonies of *Aspergillus*, while immunohistochemistry was strongly positive for PCP. Notably, at that time, the patient was still afebrile with no chest symptoms or signs. However, he was unable to get himself on or off the bed, despite physiotherapy, and his nutritional status was poor.

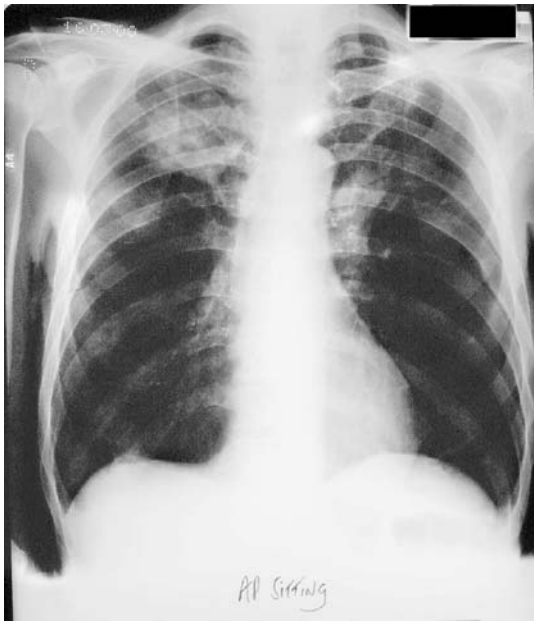

Fig. 1 Bilateral cavitating lesions in the anterior upper lobe

The patient was started on amphotericin B (1 mg/kg) and HAART consisting of stavudine, didanosine and efavirenz. Shortly after the initiation of antifungal therapy and HAART he became febrile again; he also had decreased O_2 saturation requiring supplemental 35% O_2 and a productive cough.

Aspergillus fumigatus was grown in sputum culture. Computed tomography scan of the chest at that time revealed only a marginal decrease in the size of the cavitating lesions in both upper zones. A new chest radiograph showed bilateral interval development of diffuse interstitial shadowing (widespread consolidation), especially in the left base and right upper lobe. A V/Q lung scan demonstrated mismatched defects, and warfarin was added to the treatment regimen. Meanwhile, a blood culture had grown *Mycobacterium avium intracellulare* (MAI), and the patient was additionally treated with clarithromycin, ethambutol, ciprofloxacin, and rifabutin.

Under these circumstances the patient was poorly motivated and made little progress with physiotherapy; his condition generally deteriorated to the point that he required nasogastric feeding. His liver and spleen became palpable, with normal appearances on ultrasound and computed tomography scan, while the results of liver function tests were moderately abnormal, i.e., comparable to baseline. The patient developed an episode of cyanosis (O_2 saturation of 86% on 35% O_2) that resolved within a few minutes with no intervention. A blood culture was positive for a coagulase-negative *Staphylococcus* species. Amphotericin B was switched to itraconazole (ITZ) because of poor clinical and marginal radiological response to the initial antifungal treatment. Of note, two measurements of *Aspergillus* precipitins (specific IgG antibodies) and specific IgE conducted at a 3-week interval were negative, while total IgE and C-reactive protein levels

increased from normal to 220 kIU/l and 100 mg/l, respectively, over the same time period. The respective in vitro susceptibility test results for ITZ and amphotericin B were MIC 0.25 mg/l, MFC >16 mg/l and MIC 0.25 mg/l, MFC 8.0 mg/l.

Two days after the initiation of ITZ the patient experienced a new episode of cyanosis with an O_2 saturation of 80%. At that time, he was cachectic, tachypneic and complaining of chest pain, and a BAL culture grew *A. fumigatus* and CMV. The latter was thought to be a contaminant and not an infection, since both funduscopy and PCR of blood were negative for CMV. The patient's abdomen was generally tender. The liver function tests were still abnormal, but unchanged, and albumin was low due to poor nutrition. The patient's liver and spleen were still enlarged. A new chest radiograph showed improvement in the right apical lesion and emergence of a right pleural effusion, while a transthoracic echocardiogram showed a small pericardial effusion without evidence of vegetation. Variations in the amount of background pneumonic shadowing in both fields were revealed in subsequent chest radiographs.

Pleural fluid cytology, microscopy and culture revealed scanty pus cells and reactive mesothelial cells with no organisms or malignant cells isolated. One week following the last BAL test, ITZ was switched to voriconazole (VRC) (200 mg b.i.d.) after an induction dose of 300 mg b.i.d. The change was based on a lack of clinical improvement, persistence of fever and isolation of *A. fumigatus* in BAL, low plasma levels and intolerance to ITZ, although an improvement of the right upper-lobe lesion had been achieved despite the increase in the interstitial component bilaterally. Shortly after VRC initiation, the patient experienced new spikes of fever and increased bronchial viscid secretions; he was becoming slightly confused and exhibiting some paranoid behavior. At that time, the CD4+ cell count had risen to 340/µl and the viral load had decreased to 10^3 copies/ml. CSF was clear, colorless and negative for pathogens and galactomannan antigen. Computed tomography and magnetic resonance imaging scans of the brain were unremarkable. The patient was having difficulty expectorating mucus, and suction revealed very thick mucus plugging.

After a 2-week course of VRC in combination with anti-*Mycobacterium avium* complex (MAC) agents, warfarin and cefotaxime, the patient's condition progressively deteriorated and he expired with breathlessness. For most of the duration of VRC treatment, he remained febrile with temperatures spiking as high as 39°C. On a chest radiograph performed on the day of death, the left lung appeared to have collapsed while a new complete left-sided opacification was visible and right upper-lobe shadowing was reduced (Fig. 2).

Lung examination during autopsy revealed massive bilateral consolidation, large bilateral pleural effusion and bilateral mucus plugging. Macroscopically, the rest of the patient's body was normal. The larynx and trachea contained viscid mucus. There was 1.5 l of serous effusion in each pleural cavity. The right lung showed a cavitating necrotic mass in the right upper lobe. The left lung also showed a small cavitating mass in the upper lobe. Both lungs were consolidated. There was no evidence of a pulmonary embolus. The pericardium contained serous fluid amounting to 250 ml. The brain was not examined. Histology confirmed invasive aspergillosis (IA) in both lungs. Granulomata were also present in both lungs. Ziehl-Neelsen staining and immunohistochemistry for *P. carinii* were negative. Multiple granulomata were also found in liver, spleen and paraortic lymph nodes, and histology results for alcohol and acid-fast bacilli were negative. There was no evidence of lymphoma.

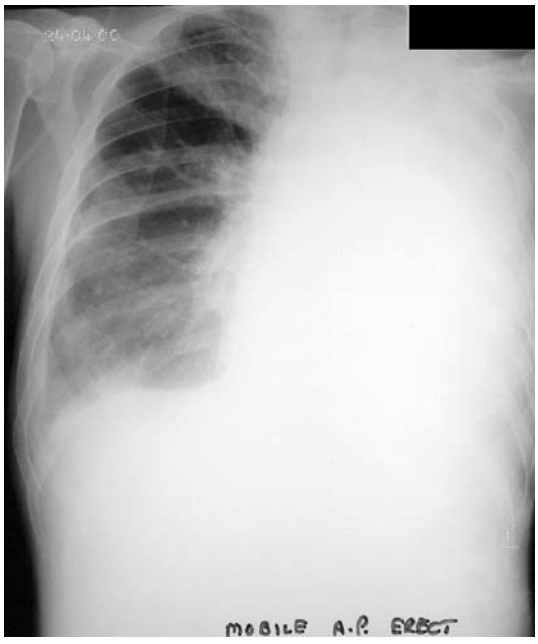

Fig. 2 Collapse of the left lung with complete left-sided opacification

Discussion

The pathogenesis of IRS has not yet been clearly defined, but immunological changes as a consequence of antiretroviral therapy have been recognized. Regeneration of naïve T cells is known to play the major role in late reconstitution of the whole CD4 subset and it contrasts with the very slow and weak regeneration observed in the naïve T cells of adults following chemotherapy or bone marrow transplantation [7]. HAART also increases CD8+ lymphocyte counts, which may account for IRS reactions, at least in part. Domingo et al. [8] showed that an increase in CD8+ T lymphocytes in response to initiation of HAART was found to be the only risk factor for herpes zoster infection in patients with HIV. Other authors have suggested the increase in CD8+ T lymphocytes after HAART initiation may result in clinical hepatitis caused by type B and type C viruses. The pathogenesis of some IRS reactions may also be cytokine-mediated. Moreover, recent data show that patients with CMV-associated IRS

are more likely to carry HLA-B44, which suggests some patients may have a genetic predisposition for developing IRS [9].

In addition to causing quantitative increases in various parts of the immune system, HAART has been shown to result in functional improvements. However, the relative importance of adaptive versus innate immune response in protecting AIDS patients against opportunistic infections remains unclear.

Prior to the case reported here, no deaths caused by IRS have been reported among HIV-positive patients, which indicates there is an overall excellent prognosis for patients who continue both ART and specific therapy for OIs. In contrast, there have been reports of deleterious and occasionally fatal effects of inflammatory or immunopathological damage related to restitution of the immune system among immunosuppressed HIV-negative patients. This phenomenon is primarily confounded by the lack of highly effective antifungal or antiviral therapy against certain pathogens such as *Aspergillus* and *Candida* spp., and hepatitis and respiratory viruses, respectively, which are the most common IRS-related pathogens affecting non-HIV-infected immunocompromised patients [10].

The differential diagnosis of cavitary pulmonary lesions in HIV-infected individuals is broad and includes invasive pulmonary aspergillosis (IPA), PCP, pulmonary cryptococcosis, coccidioidomycosis, histoplasmosis, tuberculosis (with elevated CD4+ cell counts), *M. kansasii* infection, pneumonia due to *Pseudomonas aeruginosa*, *Nocardia asteroides*, and *Rhodococcus equi* and, rarely, non-infectious causes. Although our patient had an antemortem culture that was positive for MAI, and granuloma formation was observed in autopsy samples of lung, liver and spleen and paraortic lymph nodes, neither alcohol nor acid-fast pathogens were detected. Moreover, only *M. kansasii* causes pulmonary infection, while other atypical mycobacteria, such as MAI, present as fever with positive blood cultures. Although PCP is included in the differential diagnosis of cavitary disease of the lung in AIDS, cavitation is uncommon in the absence of other pulmonary pathogens or malignancy, and it is sometimes secondary to bronchoscopy, aerosol pentamidine therapy and mechanical ventilation. In the case of our patient, antemortem immunochemistry was strongly positive for PCP, but no evidence of it was found during the autopsy. It should be noted, however, that organisms persist in clinical specimens for days or weeks after effective therapy.

Despite the difficulty in interpreting the precise etiology of our patient's lethal outcome, IPA was a documented antemortem diagnosis and the only autopsy finding. Pulmonary symptoms, along with characteristic bronchial viscid mucus, were the predominant features leading directly to death, with other variables contributing to a lesser degree. It would not be surprising if a MAC-related IRS with extrapulmonary involvement also contributed to the fatal outcome in this case, since the simultaneous occurrence of two HIV-related immune reconstitution diseases after HAART initiation has been reported previously [11].

Although the incidence of aspergillosis in HIV-positive patients remains low in contrast to that in other immunocompromised patients, it carries a high risk of morbidity and mortality. There are conflicting data about predisposing factors: Although neutropenia and the use of high-dose steroids have been reported as major predisposing factors in the general population, along with alcohol consumption and marijuana use, these factors are absent in many HIV-positive patients with IPA. Pre-existing pulmonary infections, including PCP, CMV, *M. kansasii*, *P. aeruginosa*, *Legionella pneumophila*, *Haemophilus influenzae* and pneumococcal pneumatocele, may predispose AIDS patients to the development of IPA through impairment of pulmonary macrophage function [12, 13]. Non-Hodgkin's lymphoma and Kaposi's sarcoma involving the lungs have also been reported as factors predisposing individuals to IPA [14]. In our case, prior PCP and steroid use as adjuvant anti-PCP therapy might have been contributing factors. Although impaired T-cell immunity predominates in HIV-positive patients, recent in vitro studies suggest macrophage phagocytosis in this population is impaired [15], and this is the most important predisposing factor for *Aspergillus* infection. As trends in the AIDS population change, re-evaluation of the epidemiology of IPA is needed. An increase in the incidence of pulmonary aspergillosis among HIV-positive patients, according to recent reports, may be attributed to (i) the prolonged survival of patients with low CD4+ cell counts and prior pulmonary OIs and (ii) neutropenia secondary to chemotherapy due to a high incidence of lymphomas reported recently in this population. Nevertheless, improvements in ART and antifungal therapy could reduce the incidence of IPA.

Although invasive aspergillosis (IA) has not been previously described in the setting of IRS in AIDS, infections due to *Aspergillus terreus* have been described in HIV-negative immunocompromised patients [10] soon after the recovery of adaptive and innate immunity, as part of an immune reconstitution syndrome. The ultimate outcome was fatal in the majority of cases despite the concomitant use of inhaled or systemic steroids. Pulmonary aspergillosis is the usual form described in AIDS, with the whole spectrum of radiological patterns having been reported. Cavitary upper lobe disease resembling semi-invasive or chronic necrotizing pulmonary aspergillosis has been seen in immunocompetent patients or in those with non-specific alterations in immune function, such as sarcoidosis, malignancies and alcoholism. Progression to disseminated disease is uncommon; however, the rate of local progression has been reported to be quite rapid, which is unusual in HIV-negative patients. Focal alveolar opacity, similar to that seen in IA, with a stable radiological picture of several-months duration and a good prognosis, has also been reported. Bilateral alveolar or interstitial disease similar to that in IA has been described as a marker for disseminated infection associated with high mortality. Airway disease, as well as bilateral pneumothoraces and pleural-based disease, have also been described [13, 16]. However, the air-crescent sign, which is a characteristic noted in up to 93% of non-HIV-infected immunosup-

pressed patients, was infrequently reported in HIV-infected patients. Mylonakis et al. [12] reported more than one coexistent finding in 18 of 44 cases, most of which were bilateral with combinations of cavities and infiltrates/opacities.

IPA has been reported to be the first manifestation of AIDS, and *A. fumigatus* is the most common species detected. Serologic methods and PCR for the diagnosis and monitoring of IPA in AIDS patients have been disappointing in comparison with studies in other immunocompromised patients [12]. The often coexisting non-specific symptoms, laboratory and imaging findings and concomitant OIs dictate that an aggressive approach with biopsy is necessary for diagnosing IPA in this population and better epidemiological data is required. One recent report indicated the infection's non-specific radiological appearance dictates the need for supportive clinical information and the expert opinions of clinicians and radiologists in order to diagnose IPA in AIDS [17].

As expected, the organisms previously involved in IRS in a variety of immunosuppressed patients, including HIV-positive individuals, were either slow growers, such as *M. tuberculosis* and *Cryptococcus* spp., or opportunistic pathogens of relatively low virulence, such as MAC, *Aspergillus* spp. and *Candida* spp. No pyogenic bacterial infections have been reported in cases of IRS to date. Moreover, patients with a low microbial burden and an orderly recovery of the immune system may have only subclinical IRS, leading to a missed diagnosis. Accordingly, only patients with a significant microbial burden and a relatively fast immune recovery may then have clinical expression of IRS. Factors affecting the onset and severity of IRS have not yet been clearly defined.

Therapeutic guidelines for IRS in AIDS are not well established and the ideal treatment has not yet been defined. Given the diversity and sporadic presentation of these reactions, it is difficult to conduct controlled trials and make recommendations regarding therapy. Some authors suggest OIs should be treated first and then, after a few weeks (which is not a well-defined interval), when a patient is clinically stable, ART should be started. This mirrors the procedure currently recommended for HIV-positive patients coinfected with tuberculosis. The use of appropriate and specific antimicrobial agents is crucial. Anti-inflammatory agents, such as nonsteroidal drugs and local or systemic steroids, seem to give promising results in terms of arresting the acute inflammatory damage that occurs during IRS in HIV-positive patients presenting with conditions such as focal MAC adenitis and IRS-related tuberculosis. However, the results of steroid use for hepatitis flare-ups induced by chemotherapy withdrawal have proved disappointing in patients with hepatitis B, unless high doses of steroids have been used in the early stage of exacerbation [18]. Since interleukins and cytokines have an apparent role in IRS, immunomodulation should be the future approach.

Diagnosis of IRS is never simple or straightforward, since there are no clinical or laboratory tests that are specific for it. Therefore, IRS is a diagnosis of exclusion. During immune reconstitution any paradoxical worsening of clinical symptoms and signs should be carefully investigated. However, such presentations may also result from inadequate antimicrobial therapy, development of drug resistance, superinfection by other organisms, or development of non-infectious complications. In the case of our patient, although potential drug-drug interactions, which is a main problem of the azole class, could have led to suboptimal antifungal treatment (e.g., co-administration of efavirenz, rifabutin and warfarin with VRC requires drug monitoring and VRC dose adjustment), azole levels in serum were measured to confirm that therapeutic levels were maintained. As an emerging clinical entity, IRS merits further study to optimize management. Awareness of IRS is required for detection of the syndrome, which is characterized by its diverse etiology and clinical expression, and only when awareness and detection are high will it be possible to determine the condition's real incidence and trends.

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