Weight loss and diabetes are new risk factors for the development of invasive aspergillosis infection in non-immunocompromized humans

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Abstract

Well-established risk factors for aspergillosis include HIV, cancer, recent corticosteroid (prednisone) therapy, chemotherapy, or thoracic surgery. Non-established risk factors may include weight loss and a history of diabetes.

Twenty-three patients without the classical risk factors for IA were identified retrospectively at Harbor UCLA Medical Center by discharge diagnosis over a 20 year period (1992-2012). None of the well-known risk factors are for Invasive Apergillious (IA).

A history of weight loss was seen in 66% of the patients with IA (15 of 23). The weight loss ranged from 3.3 lbs to 43 lbs. In patients with weight loss the average loss was 22±3 lbs (mean ±SEM). In this small group of patients with IA, diabetes was seen in 8 of the 23 (34%), which is significantly higher than the 19% incidence of diabetes seen in 100 patients with severe sepsis (p<0.05). Likewise, the 34% incidence of diabetes was higher than the 21% incidence reported in immunocompromised patients with invasive aspergillus (IA) infection (p<0.05). A reduced serum albumin concentration was seen in 33% of the study patients, which was less common than the 87% incidence seen in patients with severe sepsis or candidaemia (54%). Seventeen of the 23 patients had pulmonary involvement. While no one had a well-established risk factor for aspergillious, four patients had alcoholism as a potential risk factor. Eleven of the 23 (48%) died during the hospital stay despite antifungal therapy. Immunocompromised patients are known to have a mortality rate of approximately 45% for pulmonary or disseminated disease.

Conclusion—The incidence of diabetes was greater than seen in immunocompromised patients and may be considered an additional risk factor for the development of aspergillois infection. In addition, a history of weight loss should increase the suspicion for the diagnosis of IA in otherwise a non-immunocompromised patient. Early recognition and treatment of aspergillosis in the non-immunocompromised patient may improve outcome. Weight loss and diabetes should be added to the list of well-known risk factors for invasive aspergillosis and its high mortality rate.

Keywords

malnutrition; weight loss; cachexia; diabetes; albumin

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Introduction

Aspergillus has many species, the most common being Aspergillus fumigatus, Aspergillus flavus, and Aspergillus niger. Any of these species may cause hypersensitivity of the respiratory tract, saprophytic involvement of the pulmonary cavities, or invasive pulmonary disease and disseminated infection. Documented common presentation of pulmonary aspergillosis includes dyspnea, fever, cough, and hemoptysis. Invasive aspergillosis typically develops in immunocompromized patients but it can occur in the immunocompetent appearing host [1].

While weight loss is common in TB, there is very little data on the importance of obtaining a detailed weight history in patients with Invasive Aspergillosis (IA).

During the Hassan J. Tabbarah Morbidity and Mortality Conference in 1992 a 42-year old man with type 2 diabetes mellitus presented with "acute pneumonia" and a 30-lb weight loss. This is the sentinel case of a non-immunocompromized patient who died with severe weight loss. After 3-weeks of antibiotic therapy for pneumonia, IA was diagnosed only made after needle aspiration of his eye. A day later the patient died. At autopsy he had IA infection of the brain, eyes, muscle, lung and other tissues. History of weight loss and diabetes should be considered two formal risks factors for IA in non-immunocompromised patients. This study was undertaken to document the incidence of weight loss, diabetes and other factors that may help identify those otherwise non-immunocompromised patients at risk for IA.

In addition to weight loss, the presence of diabetes may also be an important risk factor for the development of IA. For example, diabetic patients have an 8.4-fold increase risk of zygomycosis (A.K.A. Mucormycosis) infection [2]. It would not be unusual for diabetes to be a risk factor for other fungal infections such as IA. Approximately 39% of the patients with zygomycosis and 21% with invasive aspergillus infection had diabetes [2]. In the current study, approximately 34% of our patients with invasive aspergillus (IA) infection also had the diagnosis of diabetes. While diabetes is believed to increase risk for many bacterial infections, it is not an established risk factor for IA. Likewise, a reduced serum albumin (<3.0 gm/dl) has been associated with an increased odds ratio (3.7–fold) for zygomycosis infection [2]. Therefore, serum albumin, weight loss and diabetes were evaluated as potential risk factors for the diagnosis of IA.

Methods

In 1992, our sentinel case introduced the hypothesis that weight loss may be commonly associated with Invasive Aspergillus (IA) infections in other wise non-immunocompromised patients. Because of this case we initiated a review of all documented cases of IA without classical risk factors: high dose glucorticoids for over 1-month, endogenous hypercortisolemia, recent thoracic surgery, active autoimmune diseases, persistent granulocytopenia or neutropenia (<500 cells/mm^3), AIDS or recent chemotherapy [1].

Twenty-three patients without the classical risk factors for IA were identified retrospectively at Harbor UCLA Medical Center by discharge diagnosis over a 20 year period (1992-2012).

None of these patients were on immunosuppressive medications nor did they have HIV or recently undergone chemotherapy. After the diagnosis of IA, one patient was diagnosed with Stage 2B colon cancer without positive nodes or metastasis and one patient was also diagnosed with adenocarcinoma of the lung. Six of these patients had a history of TB treated in the past. Nine of the 23 (39%) had a history of diabetes, four were on oral medications, and the other five were on diet alone. This study was approved by the IRB.

Weight, height and history of weight loss were obtained from the medical records. If usual weights were not available from the hospital record, we estimated the patient's usual body weight as the patient's ideal body weight based on the patient recorded height and sex. Autopsies were performed on eight of the patients, which confirmed the presence of invasive IA. Bronchoscopy, (n=9), needle aspirations (n=2) and other biopsies (n=4) were obtained to confirm the diagnosis of IA.

The non-immunocompromised patients were compared to 100 septic patients reported earlier [11] and compared to patients with candidemia [3]. The incidence of diabetes, serum albumin <3.0 gm/dl, neutropenia (<500), weight loss, body weight, age and sex were compared by T-testing and by Chi squared testing. Both the current cases and the comparative published data [7] were treated with amphotercin B due to the fact that newer agents for IA (such as voriconazole) were not utilized at that time.

Results

Patients with IA had a significantly lower body weight than patients admitted to the same hospital with severe sepsis (Table 1). Thirty four percent of the patients with IA had diabetes, which was significantly (p<0.05) higher than the 19% reported in the 100 patients with sepsis (Table 1) or in 144 patients with immunocompromised IA (Table 2).

In the current study, 65% (15 of 23) of patients had a history of weight loss with an average weight loss of 22±3 lbs (mean±SEM). The duration of weight loss was between 6 weeks and 6 months for all but one patient who lost weight. One patient had a 100 lb wt loss over the preceding 4 years. Of the 8 patients without known weight loss, there was no documentation of body weight or weight loss in the medical record in two patients. In the other six patients there was documentation that there was no history of weight loss.

Serum albumin was <3.0 gm/dl in 6 of the 18 patients (33%). Serum albumin was not measured in 5 patients. An albumin <3.0 gm/dl seen in only 33% of the patients was significantly less common than the 87% incidence seen in patients with sepsis (Table 1). Likewise, the 33% incidence of hypo-albuminemia was not significantly different than the 54% reported for candidemia (54%, Table 2). Neutropenia was significantly less common (0 vs. 45%) than seen in immunocompromised patients with IA but not less than seen in patients with candidemia (Table 2). Another classical marker of protein malnutrition is a reduced total lymphocyte count being under 1500 cells/ml. A reduced lymphocyte count was seen in 50% of the patients (10 of 20 patients). Total lymphocyte counts were not available on three patients. As expected, neutropenia (neutorphil <500) was not seen in any of the 23

cases in this report. In contrast, this has been reported to be seen in approximately 45% of immunocompromised patients with IA [8].

Seventeen of the 23 patients had pulmonary involvement as confirmed by biopsy or at autopsy. Eleven of the 23 died in hospital. Twenty-one of the 23 patients had either a history of weight loss, diabetes or a reduced total lymphocyte count. Mortality was similar between IA patients who were immunocompromised [8] and the current set of non-immunocompromised patients (42% vs. 48% mortality; Table 2).

Discussion

None of the classical risk factors were present in this group of patients with IA. Potential risk factors in this group included four patients with ethanol intake and two patients with malignancy. However, none of the patients had classical risk factors for IA. While weight loss is common in the immunocompromised cancer patients undergoing chemotherapy, its use may provide for an inexpensive and helpful risk factor to suspect the diagnosis of IA. Most of these patients, like in the sentinel case, died due to the lack of suspicion for the early diagnosis of IA.

Approximately two-thirds of the cases had weight loss prior to the diagnosis of IA. Weight loss was likely a result of IA because there were no other common factors that could explain weight loss prior to infection, such as poor diabetic control, gastric bypass surgery, etc. While no studies have documented weight loss prior to diagnosis of IA, a recent paper has demonstrated that approximately two-thirds of patients with IA a reduced albumin [2]. An albumin <3.0 gm/dl was associated with a 3.7-fold increase in mortality (44.4% vs. 12% mortality). Likewise, a reduced serum albumin has also been recently reported to be a marker of hospital mortality in patients with candidaemia [3]. The average albumin in those who died was 2.5 gm/dl as compared to 3.0 gm/dl in those who survived. In a multivariate analysis, albumin concentration was directly related to survival. For every gram decrease in serum albumin, the mortality rate increased 1.58-fold [3].

Serum albumin is an excellent marker of 30-day hospital survival in surgical patients [4] and in a mixture of medical and surgical patients (Tayek, unpublished observation, mortality=32/albumin^2). A reduced serum albumin concentration is a reflection of greater inflammatory response to infection. It is well known that TNF alpha, increased secondary to infection, inhibits albumin gene transcription. This is the most likely explanation for the reduced serum albumin concentration observed in patients with severe infection. Therefore, while albumin is used in the literature as a marker of malnutrition, in the infected host it likely reflects the livers inability to make albumin. The fact that only 33% of the cases had a reduced serum albumin, and many more with sepsis or candidaemia have a reduced albumin, deems little usefulness for a use of a reduced albumin as a marker of IA.

Weight loss that occurs in patients with TB and other chronic infection reflects a failure of dietary intake to maintain an adequate nutritional status. Unlike serum albumin concentration, which can decrease overnight due to injury or infection, the loss of muscle and fat only occurs after a sustained period of time. A prolonged fungal infection, such as

IA, will reduce serum albumin if the injury response is large, but if it is slow and persistent, then the host may only lose weight and serum albumin concentrations may be maintained >3.0 gm/dl. Unexplained weight loss should raise the suspicion for IA as it has in the past for the diagnosis of TB. Weight loss has been reported to be seen in 15 of 15 immuno-compromised patients [9] and in 1/3 of immunocompetent patients with pulmonary aspergillus nodules [10].

Besides weight loss and serum albumin, the presence of diabetes may be an additional major risk factor for IA. In the current study, eight of the 23 patients (34%) had the diagnosis of diabetes (or had developed new-onset hyperglycemia upon presentation). The 34% incidence of diabetes in patients with IA is significantly greater than that seen in severe sepsis [11] or in candademia [3]. However, the 34% incidence was based on a very small sample size which is subject to verification. In another study of IA, the incidence of diabetes was seen in only 15% but the odds ratio for mortality was increased 8.4-fold [2].

It is well known that new onset hyperglycemia (elevated fasting blood glucose or non-fasting glucose >199 mg/dl) increases hospital mortality 9.4-fold as compared to non-diabetic patients (16 vs. 1.7% mortality) [5]. Likewise, hyperglycemia also increases ICU mortality risk by approximately 3-fold [6]. Whether the elevated blood glucose associated with the diagnosis of diabetes increased the risk of IA or was a marker of the body's inflammatory response to IA is unknown.

In the immunocompetent host, invasive pulmonary aspergillosis can progress to pneumonia and death within several weeks. In mice infected with invasive aspergillosis, weight loss is universal and is preceded by mortality [12]. The ability to obtain a weight loss history may be an excellent marker for the early identification of patients who may be a higher risk for IA. Earlier diagnosis and treatment for IA may reduce mortality associated with this disease.

Lastly, a commonly obtained lymphocyte count in non-HIV patients may also be a good marker of IA. In an older study, 14 of the 16 patients with IA had a total lymphocyte count less than 1500 [7]. In the current study, 50% of the patients had a total lymphocyte count less than 1500. Therefore, weight loss, diabetes and a reduced lymphocyte count should increase ones concern for the diagnosis of IA.

As the mortality rate of pulmonary or disseminated disease in the immunocompromised patient remains around 40%, early recognition and treatment of aspergillus may be the difference between life and death. While survival of this disease has recently improved with the use of Voriconazole versus conventional therapy with amphotericin therapy [8-12], the mortality rate is still elevated. If the diagnosis is missed after more than a month in the hospital, the mortality rate will likely be quite high as in our sentinel case. Increasing the clinicians understanding that weight loss and a reduced serum albumin reflects a chronic process such as fungal (IA) infections, may potentially identify unusual IA infection in an otherwise non-susceptible host. Recent work would suggest that aspergillus nodules can have one-third in immunocompetent patients with weight loss [10].

Acknowledgments

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Table 1

Patient characteristics

(n)	Age (yrs)	Sex (%male)	Admit Wt (lbs)	Diabetes (% yes)	Albumin (<3.0gm/dl)
Severe sepsis patients (Published Data; Reference 9)					
(100)	51±14	67%	167 ± 18	19%	87%
Current Immunocompetent Patients					
(23)	53±16	56%	128 ± 6 *	34% #	33% #

*
p<0.05 by T-testing

#
p<0.05 by Chi Square Testing; Mean±SEM

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Table 2

Patient Characteristics with Fungal Infections

(n)	Age (yrs)	Sex (%male)	Usual Wt(lbs)	Admit Wt(lbs)	Hx Wt Loss	Diabetes (% yes)	Albumin (<3 gm/ dl)	Neutropenia (<500)	Mortality (%)
Current Non-immunocompromized Patients									
(23)	53±16	56%	141 ± 7	128 ± 6	65%	34% [#]	33% [^]	0% [#]	48%
Immunocompromized Patients with Invasive Aspergillus Infections (Published Ref 8)									
(133)	51	67%	NR	156	NR	NR	NR	45%	42%
Immunocompromized and Non-Immunocompromized Patients Candademia Infections (Reference 3)									
(288)	45	51%	NR	NR	NR	21%	54%	12% [^]	36%

(mean±sem),

[#]
p<0.05 by Chi Square Testing

[^]
p=0.10, Not significant

NR Not Reported

SEM for ages not reported (Ref 3 and 8).