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Surgical management of invasive pulmonary aspergillosis in immunocompromised patients

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Abstract. The treatment of haematological malignancies with intensive chemotherapy and bone marrow transplantation results in prolonged periods of immunosuppression. This is associated with an increased incidence of invasive pulmonary aspergillosis (IPA) with reported mortalities of 67–83%. The mainstay of treatment is medical therapy, surgery being reserved for patients with haemoptysis. Resection of focal sites of infection has not been routinely considered in view of the high morbidity and mortality reported from the surgery of aspergillomas in past series. After the death of two neutropenic patients from massive haemoptysis following IPA in 1986, we have resected localised pulmonary aspergillus lesions in 16 patients following IPA. Five patients had haemoptysis. The most common procedure performed was a lobectomy. All patients were granulocytopenic and excessive post-operative bleeding occurred in three patients, one of whom required a re-thoracotomy as a result. There was one post-operative death due to cytomegalovirus pneumonia. Surgery was otherwise uneventful. There were no recurrent pulmonary aspergillus infections on follow-up and three patients proceeded to bone marrow transplantation. The success of surgical resection encourages an aggressive policy in the management of IPA to prevent life-threatening haemoptysis and to allow patients to proceed with further chemotherapy and bone marrow transplantation. [Eur J Cardio-thorac Surg (1992) 6:138–143]

Key words: Invasive pulmonary aspergillosis – Surgical management – Immunocompromised bone marrow transplantation – Haemoptysis

The use of intensive chemotherapy and bone marrow transplantation in the treatment of haematological malignancies renders patients severely immunocompromised and suffering a high incidence of opportunistic pulmonary infections. Invasive pulmonary aspergillosis (IPA) is common among these patients and has a reported incidence of 20% [23] with a mortality of 67–83% [1, 8]. IPA may manifest as cavitating lesions similar to complex aspergillomas, with thick-walled cavities, surrounding parenchymal disease and haemorrhagic pulmonary infarction. The treatment of these focal lesions has conventionally been medical because of the high morbidity following surgical resection of complex aspergillomas [3, 7, 12]; surgical resection is often reserved for patients with haemoptysis. Since the death of two neutropenic patients in our haematological unit from massive haemoptysis following IPA we have routinely resected such localised lesions. As there are few reports on the surgical management of IPA in the literature [2, 14, 20], we report on our recent experience.

Patients and methods

The case records of all patients with IPA who had surgical treatment at the Royal Free Hospital between January 1986 and July 1991 were reviewed. Sixteen patients were identified, all being treated for haematological malignancies. Two of these patients have been previously reported in the literature [14].

The records were reviewed for the stage of illness, length of neutropenia, presenting symptoms and signs, diagnostic investigations, site of lesion, preoperative medical treatment and surgical procedures performed, perioperative blood loss and the quantity of blood and platelets transfused, the postoperative course and complications and the duration of intercostal chest drainage. The histology and parasitology and the patients subsequent progress, were also reviewed.

Results

Of the 16 patients 10 were male and 6 female. Their ages ranged between 16 and 57 years, with a median age of 26

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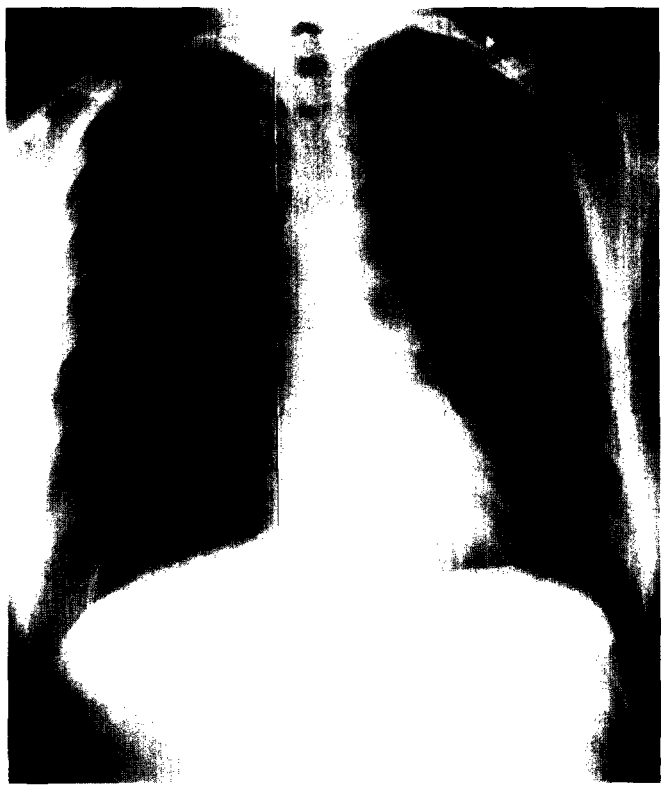

Fig. 1. Chest roentgenogram showing the typical air crescent sign in a 31-year-old with cavitating IPA in the left upper lobe

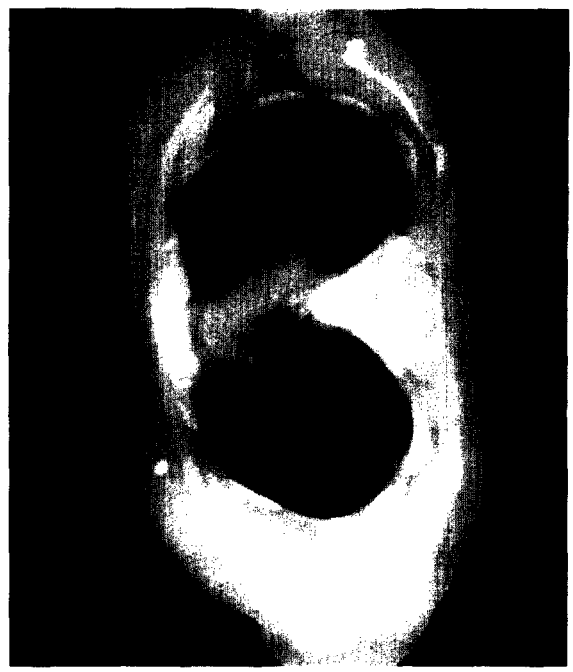

Fig. 2. Computer tomography of the chest in the same patient. The cavitating lesion in the left lung is characteristic, with a central mass (sequestrum) and surrounding parenchymal disease. A second mass lesion with a surrounding halo of low attenuation can be seen in the contralateral lung

Table 1. Clinical features of the 16 patients with invasive pulmonary aspergillosis (IPA)

	No. of patients
Age (years)	
median	26
range	16–57
Sex	
male	10
female	6
Underlying disease/condition	
acute lymphoblastic leukaemia	6
acute myeloblastic leukaemia	4
chronic granulocytic leukaemia	2
lymphoma	2
bone marrow recipient (ALL)	2
Period of neutropenia ($<0.5 \times 10^9$/l)	
mean (days)	22
range (days)	15–30

ALL = acute lymphoblastic leukaemia

Table 2. Symptoms and signs in the 16 patients with IPA

	No. of patients
Pyrexia	15
Cough	6
Haemoptysis	
major (>100 ml/day)	1
minor (<100 ml/day)	4

years. Twelve had undergone chemotherapy for leukaemia and two for lymphoma (Table 1). Two patients had undergone allogenic bone marrow transplantation for leukaemia. All were immunocompromised at the time of infection and had been neutropenic (granulocytic count $<0.5 \times 10^9$/l) for an average of 22 days (range: 15–30 days). Pulmonary cavitation occurred following bone marrow recovery in 13 patients.

Pyrexia was the first sign of infection in 15 patients (Table 2). Temperatures were persistent and ranged between 37.8 °C and 39.0 °C. Five patients had haemoptysis. One had a major haemoptysis episode (>400 ml) while the other four had minor episodes (<100 ml/day). The patient with a major haemoptysis was cardiovascularly compromised and required emergency surgery. The aspergillus lesion was found to involve a major pulmonary vessel.

The diagnosis of IPA was suspected on chest roentgenogram and computer tomography (CT); a definitive diagnosis can only be made by culture and histological examination of the tissue specimen. Chest roentgenograms showed the classical air crescent sign consistent with cavitating lesions (Fig. 1) in 13 patients, whilst 3 patients had nodular shadowing. Three patients had pneumonic changes before the appearance of well-defined lesions. CT confirmed cavitating lesions with surrounding parenchymal involvement (Fig. 2) in all patients. CT revealed a second lesion not seen on chest roentgenograms in two patients. These lesions were non-cavitating and showed a mass-like infiltrate surrounded by a halo of low attenuation. Only 1 of the 16

Table 3. Radiological findings and site of lesions in the 17 patients with IPA

	No. of patients
Roentgenographic findings	
air crescent sign	13
mass shadowing	3
CT scan findings	
cavitation	16
non-cavitating/mass infiltrate (second lesions)	2
Site of lesions	
upper lobe	15
middle lobe	4
lower lobe	4
two unilateral lesions	5
bilateral lesions	2

Table 4. Surgical procedures performed and post-operative complications and mortality in the 16 patients with IPA

	No. of patients
Initial procedure	
lobectomy	15
pneumonectomy	1
wedge resections	3
Second procedure	
re-thoracotomy for bleeding	1
completion pneumonectomy	1
Complications and mortality	
bleeding	3
death from respiratory failure (cytomegalovirus pneumonia)	1

patients had a positive sputum culture. Bronchial lavage performed on three patients and fine needle aspiration on one patient gave negative results. The most common site of these lesions was in the upper lobe. Five patients had multiple lesions and two bilateral lesions (Table 3).

Surgery was undertaken by a single surgeon (R.K.W.). Lobectomies were performed in 14 patients (bilateral in one patient) and pneumonectomies in two patients, in one of whom the operation was a completion pneumonectomy after the detection of a second lesion shortly after the original operation. Wedge resection were performed in three patients (Table 4).

The average operative blood loss was 600 ml (range: 50 ml–1.4 l) and the immediate postoperative chest drainage (12 h) averaged 577 ml (range: 100 ml–2.5 l). The amount of blood transfused averaged 4 units (range: 2–4 units). The average preoperative platelet count was 88×10^9/l (range: $9-310 \times 10^9$/l) and patients were given an average platelet transfusion of 13 units perioperatively. Coagulation studies were normal in all patients. There were problems of perioperative bleeding in three patients, one of whom required a second thoracotomy as a result. No specific bleeding point was identified in this case. In the other two patients, the dissection was difficult because of the close proximity of the lesion to a pulmonary artery and the oedematous surrounding tissue. The latter seemed to be a common finding at operation and made dissection difficult.

The average length of intercostal chest drainage following surgery was 5 days (range: 2–7 days). There were no problems with prolonged air leak. There was one postoperative death from respiratory failure due to the progression of cytomegalovirus pneumonia. The patient had developed a cavitating lesion following bone marrow transplantation. Pathological examination of the resected lung, however, revealed aspergillus fungus and cytomegalovirus inclusion bodies. Surgery was otherwise uneventful.

The mean period of follow-up was 11 months (range: 3–36 months). Three patients have since undergone bone marrow transplantation. Six patients including two who received transplants have since died from their original disease or related complications. None of our patients has had a recurrence of pulmonary aspergillosis.

Aspergillus species were cultured from the resected lung tissue in all patients. *Asp. fumigatus* was found in 12 patients, *Asp. flavus* in 3 patients and *Asp. terreus* in 1 patient. Histological appearances were consistent. Macroscopically, these showed a haemorrhagic area with central cavitation and a necrotic mass within. The surrounding lung often showed small areas of pulmonary infarction. Microscopically, hyphae invasion, thrombosis of pulmonary vasculature, areas of infarction and chronic inflammation were seen in the surrounding lung parenchyma. The cavities contained necrotic lung tissue with fungal hyphae.

Discussion

Aspergillus species are ubiquitous and viable spores are usually present in air. They are usually of low virulence in man. Pulmonary aspergillosis is classified into three categories: allergic, saprophytic and invasive [11]. The allergic form is due to immunological reactions to the fungus in the bronchial tree. Saprophytic disease results from the colonisation of pre-existing cavities and the lesions have been classified into simple (SA) and complex aspergillomas (CA) depending on the extent of parenchymal disease around the cavity [4]. IPA occurs almost exclusively in immunocompromised patients.

IPA may present as a necrotising bronchopneumonia or haemorrhagic pulmonary infarction. More recently, the formation of "mycotic lung sequestrum" has been described. The latter is a more accurate description of the sequestration of devitalised lung tissue within previously normal lung and highlights the difference in its aetiology from a mycetoma (fungal ball) or classical aspergilloma. These cavitating lesions were seen in all our patients. They are pathologically similar to CA and have thick-walled cavities with extensive disease infiltration into the surrounding parenchyma. It is uncertain why some patients develop pneumonic or localised nodular lesions whilst other patients develop cavitating lesions. Przyjemski and Mattii suggested that this was related to bone marrow regeneration and the return of granulocytes [18]. They hypothesised that proteolytic enzymes were released by the influx of granulocytes, which caused lysis

and separation of the sequestra from the surrounding parenchyma. This is supported by the fact that cavitation is seen more frequently in renal transplant patients who are not granulocytopenic [22]. It would also explain why some patients have radiological pneumonic changes or localised nodular lesions which progress to cavitating lesions. This was seen in two of our patients and has been observed by other authors [5, 16]. Three of our patients were, however, still severely granulocytopenic (count $<0.5 \times 10^9$/l) when cavitation occurred, whilst the remainder showed cavitation after an average of 6 days following the return of a granulocytopenic count greater than 0.5×10^9/l. Albeda et al. have also observed that some patients with marrow regeneration do not show cavitating changes [2]. The mechanism of cavitation may depend on other intrinsic host immune responses.

IPA may be clinically asymptomatic for long periods in immunocompromised patients but runs a fulminant course if not treated aggressively. The risk of developing IPA increases with the duration of neutropenia, reaching at least 70% in patients granulocytopenic for more than 34 days [10]. The average days of granulocytopenia among our patients was 22 days. Other risk factors include whether the underlying disease is in remission and the use of broad-spectrum antibiotics and steroids [21].

The disease may initially present with an unremitting pyrexia, and this was seen in all our patients. Dyspnoea and a non-productive cough is often present in the later stages.

Haemoptysis occurs in up to 52–80% of patients with classical aspergillomas [3, 7, 12, 19], but has been previously considered a rare problem in IPA. However, it is now a commonly recognised feature and an important cause of mortality in patients with IPA. It has been reported to occur in 8 of 26 patients (31%) with IPA in one haematological centre, and death occurred following massive haemoptysis in one patient [2]. These findings are similar to ours. Haemoptysis occurred in five of our patients (31%). It was usually seen after the return of a granulocytic count exceeding 0.5×10^9/l. It is possible that, like cavitation, the influx of neutrophils leads to the destruction of vascular structures, resulting in haemoptysis. Four of our patients had haemoptysis within 8 days following a granulocytic count exceeding 0.5×10^9/l, although one patient was still granulocytopenic. There were unfortunately no clinical nor radiological features which could identify patients more likely to develop haemoptysis, although other authors have observed that massive haemoptysis followed minor episodes of bleeding [2].

Early diagnosis of IPA is important if treatment is to be successful. Sputum cultures and fiberoptic bronchial lavage were unhelpful in the diagnosis of IPA in our patients: only one patient had a positive sputum culture, and bronchial lavage performed in three patients was negative. Kahn et al. have reported better success using bronchoscopic techniques with an overall positive diagnosis in 22% of their patients [13]. Thirteen patients had chest roentgenograms with an air crescent sign consistent with cavitating lesions. CT scanning was the most effective means of establishing a diagnosis, confirming cavitating lesions in all patients and detecting a second lesion in two patients. These lesions were characterised by a mass-like infiltrate with a surrounding halo of low attenuation. Kuhlman et al. reported similar lesions preceding cavitation, and it would seem that such mass lesions are early CT findings of IPA [15, 16].

The degree and duration of granulocytopenia is an important factor determining the prognosis in IPA. Mortality is approximately 40% with bone marrow recovery and 100% in the absence of marrow recovery [2]. In a large review of cases reported in the literature, the mortality from IPA in bone marrow recipients exceeded 94% irrespective of treatment [9].

It is unfortunate that death occurs in these patients at a period when their underlying haematological disease may be in remission or when they have a possible chance of cure by bone marrow transplantation. The current treatment of IPA is medical with few indications for surgery. There have been no prospective trials comparing the different modalities of medical treatment and surgical resection. Amphotericin B is the most common antifungal used and has a reported response rate of 55% [9]. Surgery has often been reserved for patients with haemoptysis.

The deaths of two patients in our haematological unit with sudden and massive haemoptysis following IPA have prompted us to adopt an aggressive policy with the resection of all localised aspergillus lesions. The aim of surgical resection is to prevent the occurrence of life-threatening haemoptysis and to eradicate the fungal infection in order to allow patients to proceed to bone marrow transplantation or further chemotherapy. Our results show that surgery can be safely performed with no recurrence of the infection which is common after medical treatment. Surgery in patients with IPA does not appear to carry the high morbidity seen after that of complex aspergillomas. Daly et al. reported a morbidity of 78% among patients with complex aspergillomas [7]. The common post-operative problems were pleural space problems, bronchopleural fistulae, prolonged air leak and empyema. None of these complications occurred in our patients.

Surgery in our series has been relatively uneventful. At thoracotomy, dissection was often difficult due to oedematous hilar structures and enlarged fleshy lymph nodes. All patients were thrombocytopenic and were given perioperative platelet transfusions. However, bleeding was still a problem and was excessive in three patients; one of these patients required a second thoracotomy. There was one post-operative death from respiratory failure because of the progression of cytomegaloviral pneumonia. This woman was one of two bone marrow recipients in our series. None of the remaining patients developed pulmonary recurrences and three patients proceeded to successful bone marrow transplantation. The low rate of complications in comparison to that after resection of CA may be attributed to the younger age, good pulmonary reserve and normal pre-morbid lungs of the patients.

The role of surgery in the treatment of IPA has yet to be clearly defined and requires prospective trials compar-

ing the effectiveness of both medical and surgical treatment. We have obtained excellent results from surgery and advocate early surgery in IPA for localised cavitating lesions to prevent life-threatening haemoptysis and to eradicate the infection. This will allow patients to continue with further chemotherapy or to proceed to bone marrow transplantation.

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Discussion

Mr. K. Moghissi (*Hull, UK*). In this paper Dr. Wong and his colleagues bring to our attention an important and growing problem. I must confess, however, that I am surprised that there are so very few reports on invasive pulmonary aspergillosis when one considers the number of immunocompromised patients, excluding the HIV group.

Our personal experience with surgically treated cases concerns three patients: one with pulmonary abscesses and two with bronchiectasis and abscess. It may be that in our area such cases have been treated by chest physicians rather than being referred to surgeons. This brings us to the questions of definition and surgical indications.

I would like to ask the following questions. What is the author's definition of IPA? In their presentation they say that it may manifest itself as cavitating lesions similar to those of aspergilloma within a thick-walled cavity and with evidence of pulmonary infarction. This is, presumably, a postmortem or postresectional diagnosis and definition. How was the distinction between IPA and an aspergilloma in its classical sense made, prior to resection or was it prior to death?

The second question concerns indications for surgery. The authors have suggested that the main surgical indication is the presence of hemoptysis, but this was present in only five out of 16 patients. What were the indications for surgery in the remaining 11?

Finally, with respect to treatment, I would like to ask whether they have any experience in these cases of embolization or intracavity drainage and lavage, which has been successful in difficult cases. We ourselves have had one case.

I would like to congratulate the authors on their excellent results and to ask in conclusion what are the risks of recurrence in these patients, because presumably they could remain immunocompromised. Finally, the 11 months mean follow-up. Would you consider that sufficient, e.g., for somebody with a pneumonectomy?

Dr. Wong: To answer your first question, aspergillomas are a different clinical entity to mycotic lung sequesters. Aspergillomas are a result of the colonization of pre-existing lung cavities in patients with lung disease, for example, tuberculosis. Invasive aspergillosis occurs in immunocompromised patients who have normal lungs. Mycotic lung sequesters develop in these patients following a return of the neutrophil count to normal. These lesions contain the fungus and necrotic lung tissue.

Your second question was on the indications for surgery. Since the death of two neutropenic patients from haemoptysis following IPA we have resected all localized aspergillus infections whenever possible. Our aim was to prevent life-threatening haemoptysis and to allow these patients to proceed to further chemotherapy and marrow transplantation, which would not be possible with on-going infection.

Regarding your third question, we have not had any experience with embolization. Embolization and intracavity drainage are procedures reserved for the treatment of patients with aspergillomas who have poor respiratory reserve and are not fit for surgery. Our patients had normal pre-morbid lungs and adequate respiratory reserve, which allowed us to perform surgical resection.

Your last question was on the risks of recurrence. All patients had a second period of immunosuppression following further chemotherapy or transplantation. Any patient who had residual infection would no doubt have had a recurrence of the infection following further immunosuppression.

Dr. E. A. Rendina (*Rome, Italy*). I have one very brief comment and one question. We have a very big referral center for hematology in Rome and our colleagues have developed an aggressive attitude towards their leukemic patients in the last 2 years. They would like to let us explore surgically all their leukemic patients with unexplained lung images that do not respond to medical treatment. Therefore, we have operated on seven such patients in this period: and five had aspergillosis, one had ficomicosis, and one had tuberculosis. This last patient eventually died of generalized pulmonary infection 1 month after surgery. All our patients, excluding of course this one who unfortunately died, went on to bone marrow transplantation, and I wonder why only four of your patients had bone marrow transplantation.

Dr. Wong: Well, I have got to commend your hematologists. Sometimes getting them to do anything about chest lesions before it is too late is a problem. However, regarding the four patients, all of our patients potentially would have undergone bone transplantation if they could have. The ones who did not, had underlying disease, perhaps chronic granulocytic leukemias, and a transplant donor was not available. All four were patients who were potential candidates for bone marrow transplantation. It had nothing to do with surgery.