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Original article

Emergency and elective pulmonary surgical resection in haematological patients with invasive fungal infections: a report of 50 cases in a single centre

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ABSTRACT

Invasive fungal infections (IFI) remain life-threatening complications in haematological patients. The aim of the study was to present the experience of a single centre in the surgical treatment of pulmonary IFI. Between 1992 and 2014, 50 haematological patients with IFI underwent pulmonary resection. In 27 cases it was an emergency procedure to avoid haemoptysis (if the lesion threatened pulmonary vessels). The remaining 23 patients underwent elective surgery before new chemotherapy or stem-cell transplantation. Among these patients (median age: 54 years; range: 5–70 years), 92% had acute leukaemia and 68% were on haematological first-line therapy (receiving induction or consolidation chemotherapies). Invasive pulmonary aspergillosis and pulmonary mucormycosis were diagnosed in 37 and 12 patients, respectively. One patient had IFI due to *Trichoderma longibrachiatum*. All of the patients received antifungal agents. In the month preceding IFI diagnosis, 94% of patients had been neutropenic. At the time of surgery, 30% of patients were still neutropenic and 54% required platelet transfusions. Lobectomy or segmentectomy were performed in 80% and 20% of cases, respectively. Mortality at 30 and 90 days post-surgery was 6% and 10%, respectively. After surgery, median overall survival was 21 months; median overall survival was similar between patients with emergency or elective surgery and between the types of IFI (invasive pulmonary aspergillosis or pulmonary mucormycosis). However, overall survival was far better in haematological first-line patients or in those achieving a haematological complete response than in other patients ($p < 0.001$). In pulmonary IFI, lung resection could be an effective complement to medical treatment in selected haematological patients. **M.-L. Chretien, CMI 2016;22:782**

Introduction

Invasive fungal infections (IFI), such as aspergillosis, mucormycosis or fusariosis, are complications that occur in immunocompromised patients after cytotoxic chemotherapy for acute leukaemia or allogeneic stem cell transplant (SCT) [1] and they remain life-threatening in this setting [2].

Invasive pulmonary aspergillosis (IPA) is the most frequent filamentous IFI in neutropenic patients. Over the last 15 years, the use of new antifungal agents (e.g. new azole compounds, liposomal amphotericin B or echinocandin) has improved outcomes in these patients [3,4]. However, the key point in the management of IPA is early recognition of the disease. Indeed, in the setting of febrile neutropenia, the prompt use of CT scan (showing the halo or air-crescent signs) combined with the detection of targeted biomarkers (such as *Aspergillus* antigen or beta D glucan) has decreased the time between the first clinical signs and the diagnosis of IPA [5–7].

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Pulmonary mucormycosis (PM) is less frequent than IPA but its incidence is increasing [8], possibly due to selection by antifungal therapy [8–10]. CT scan signs are less useful in PM than in IPA. Nevertheless, in neutropenic patients, the CT reversed halo sign has been frequently described during the course of the disease and could be very helpful [11]. No biological test is available for the diagnosis of PM except the detection of circulating *Mucorales* DNA in the serum of patients [12]. First-line medical treatment of PM is mainly based on liposomal amphotericin B. Posaconazole is most often used as second line or maintenance therapy.

In pulmonary IFI, surgery can be a useful complement to medical antifungal treatment. Most often, in haematological malignancies, elective surgery is proposed to decrease or eradicate a residual fungal lesion before a new intensive chemotherapy or SCT.

Both IPA and PM are angio-invasive diseases and during the course of infection, the hyphae colonize the bronchi and the arteries and cause local infarction [13]. At the time of granulocyte recovery, proteolytic enzymes are released at the site of infection and might cause the destruction of lung tissue [14] and haemoptysis by arterial perforation when IFI involve a pulmonary artery [15]. Therefore, in this setting, surgery may be considered to avoid fatal haemoptysis.

However, publications on surgical resection in a context of pulmonary IFI are limited to a few small series, which reported variable results in terms of morbidity and mortality [16–23].

We report 20 years of experience in haematological patients with pulmonary IFI who underwent surgical resection either in emergency (prophylaxis of haemoptysis) or elective (resection of residual lesion) procedures. The local institutional review board approved the study.

Patients and Methods

From October 1991 to September 2014, 50 patients underwent lung resection for IFI complicating their haematological malignancy in the Haematology Department of Dijon University Hospital, France. This retrospective study inventoried our clinical practice concerning these IFI. Some of these patients were included in a previous report [24].

The initial diagnosis of IFI in patients with prolonged neutropenia and unresolved fever was mainly based on a prompt CT scan. Briefly, IPA was suspected when the CT showed a halo sign, whereas PM was suspected when it showed the reversed halo sign. In patients with suspected IPA, *Aspergillus* antigenaemia (Platelia Aspergillus® test) was measured (since 1997) on repeated serum samples. The most recent patients with suspected PM were screened for circulating *Mucorales* DNA. In most cases, a bronchoalveolar lavage was performed. Bronchoalveolar lavage fluid has been tested for *Aspergillus* antigen systematically since 1998. Overall, as soon as IFI was suspected, medical antifungal treatment was started and mainly consisted of voriconazole for IPA (or itraconazole during the first years of the study) and liposomal amphotericin B for PM (or amphotericin B deoxycholate during the first years of the study).

All surgeries were therapeutic and we distinguished between emergency and elective surgery. Emergency procedures were decided on when fungal lesions threatened the integrity of the pulmonary artery or its divided branches to prevent intra-alveolar haemorrhage and fatal haemoptysis (Fig. 1). This surgery was performed irrespective of granulocyte count. In contrast, when fungal infection was peripheral but persisting or even worsening despite antifungal therapy, or when eradication was necessary before a new course of intensive chemotherapy or autologous or allogeneic SCT, the surgery was delayed and elective. In this elective setting, the neutropenia had resolved at the time of surgery in most cases. For all patients, platelet transfusions were required immediately before surgery if the platelet count was <50 G/L.

Statistical analysis

Demographic and baseline clinical characteristics were described with medians and interquartile ranges or with proportions, as appropriate. chi-square test and Mann–Whitney *U* test were used as indicated. Survival was measured from 1 October 1991 and estimated according to Kaplan–Meier estimates. Group comparisons used a log-rank test (or an equivalent univariate Cox's proportional hazard model).

All statistical tests were two-tailed, and results with $p < 0.05$ were considered statistically significant. Statistical analyses were performed with Stata (version 11).

Results

Characteristics of patients at the time of IFI diagnosis

Patient characteristics at the time of IFI diagnosis are shown in Table 1. The median age of the 50 patients was 54 years (5–70 years). Acute leukaemia was diagnosed in 46 patients (36 myeloblastic; ten lymphoblastic) and the four remaining patients had multiple myeloma ($n = 2$), non-Hodgkin lymphoma ($n = 1$) or chronic lymphocytic leukaemia ($n = 1$). In 68% of cases, patients were on first-line haematological treatment (most often in the emergency group). In the month preceding IFI, 94% of patients had severe neutropenia (polymorphonuclear cells <0.5 G/L for more than 10 days). One patient had previously received an allogeneic SCT. Clinical signs in the two groups of patients were similar.

All of the patients underwent a thoracic CT scan. Bilateral pulmonary involvement was more frequent in the emergency group than in the elective group. The CT was very helpful for the diagnosis of IFI, showing the typical CT halo sign or reversed halo sign in 72% and 22% of cases, respectively.

Sequential testing for *Aspergillus* antigenaemia was performed in 40 patients and was positive in 55% of cases. A bronchoalveolar lavage was performed in 41 patients. Direct examination was positive in eight cases while culture yielded *Aspergillus fumigatus*, *Absidia* sp. and *Trichoderma longibrachiatum* in four, two and one

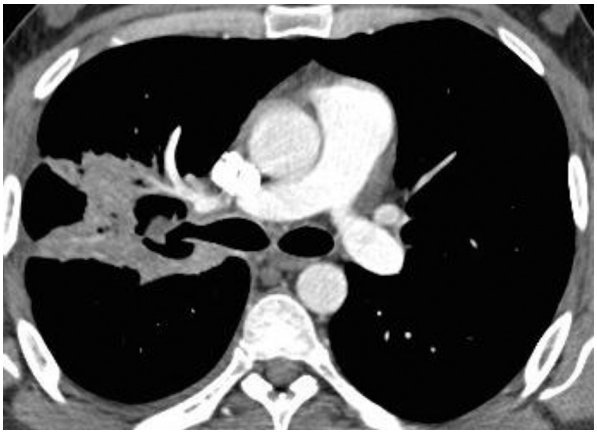

Fig. 1. Pulmonary mucormycosis occurred in a 32-year-old patient after induction chemotherapy for acute myeloblastic leukaemia. Enhanced CT scan showed involvement of divided branches of right pulmonary artery by the fungal process. In August 2012, a right upper lobectomy was performed in emergency to prevent the risk of arterial perforation and haemoptysis. Three years later patient is alive and well.