

CIRUGÍA ESPAÑOLA

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Original article

Bronchogenic carcinoma in patients undergoing solid organ transplant. The role of surgery

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ARTICLE INFO

Article history:

Received November 17, 2008

Accepted February 25, 2009

Online May 23, 2009

Keywords:

Bronchogenic carcinoma

Solid organ transplant

Surgery

A B S T R A C T

Background: The incidence of neoplastic diseases is higher in patients undergoing solid organ transplant. However, the incidence of bronchogenic carcinoma (BC) is controversial. The objective of our study was to determine the incidence of BC in a large cohort of transplant patients and the role of surgery.

Material and methods: Until December 2006, 3596 patients underwent solid organ transplant at our institution; 24 (0.7%) patients subsequently developed BC, of which 6 (24%) were classified as clinical stage I and submitted to surgical treatment. Survival was estimated by the Kaplan-Meier method.

Results: Three patients received a liver transplant, 2 a kidney transplant and 1 a heart transplant. All were male and all had a smoking history. Mean age was 58.6 years. Two patients had cough, one accompanied by bloody expectoration, and BC was an incidental finding in the remaining cases. The interval between transplant and diagnosis of BC was 38.1 months. Epidermoid carcinoma was the most frequent histological type. Mean tumour size was 3.6 cm (range, 1.3–6). One tumour was classified as pathological stage IA, 4 as stage IB, and 1 as IIB due to parietal pleural invasion. No patient died during the perioperative period and only one had a haemothorax which resolved with chest tube drainage. Mean hospital stay was 8.5 days (range, 7–11). The immunosuppression regimen was maintained continuously. In subsequent follow-up, 1 patient died from BC metastasis, 1 from sepsis, 1 from chronic renal failure, and 3 remained alive. The probability of survival at 5 years was 40%, and median survival was established at 5 years.

Conclusions: The incidence of BC in patients undergoing solid organ transplant and the proportion of patients diagnosed in early stages does not differ from non-transplant patients diagnosed with BC, which questions the role of immunosuppression in the genesis and aggressiveness of BC in transplant patients. Surgery may offer acceptable results in early stages, with acceptable rates of perioperative morbidity and mortality.

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Carcinoma broncogénico en pacientes con trasplante de órgano sólido. Papel de la cirugía

R E S U M E N

Palabras clave:

Carcinoma broncogénico
Trasplante de órgano sólido
Cirugía

Introducción: La incidencia de neoplasias es mayor en la población sometida a un trasplante de órgano sólido; sin embargo, la de carcinoma broncogénico (CB) es controvertida. Nuestro objetivo es comprobar la incidencia de CB en pacientes trasplantados y el papel de la cirugía.

Material y métodos: Hasta diciembre de 2006, en el Hospital Universitario La Fe, 3.596 pacientes recibieron un trasplante de órgano sólido; 24 (0,7%) pacientes desarrollaron un CB, de los que 6 fueron operados. La supervivencia se estimó mediante la prueba de Kaplan-Meier.

Resultados: Tres pacientes habían recibido trasplante hepático; 2, renal y 1, cardíaco. Todos eran varones y tenían historia previa de tabaquismo. La media de edad fue 58,6 años. El intervalo entre trasplante y diagnóstico de CB fue 38,1 meses. El carcinoma epidermoide fue el más frecuente. El tamaño tumoral medio fue de 3,6 cm. Un tumor fue clasificado en estadio IA patológico; cuatro, en IB y uno, en IIB. Ningún paciente falleció en el perioperatorio y sólo uno presentó un hemotórax. La media de estancia fue 8,5 días. Un paciente falleció por metástasis de CB, otro por sepsis, otro por insuficiencia renal y 3 permanecían vivos. La supervivencia a los 5 años fue del 40%.

Conclusiones: La incidencia de CB y la tasa de diagnósticos en estadios precoces no difieren de las observadas en pacientes no sometidos a trasplante, lo que cuestionaría el papel de la inmunosupresión en la génesis y la agresividad del CB en pacientes trasplantados. La cirugía puede ofrecer resultados aceptables en estadios precoces, con una morbilidad perioperatoria asumible.

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Introduction

It is well known that patients subject to a solid organ transplant run a greater risk of presenting a neoplastic disease than in the general public, which increases with survival time after the transplant as a consequence of immunosuppression therapy.¹ However, the incidence of bronchogenic carcinoma (BC) in solid organ transplant patients is controversial.² In the past decade, certain papers have manifested a high rate of BC in patients previously subject to heart transplants.^{3,4} On the contrary, more recent studies have shown a similar incidence to that displayed in non-transplant patients.^{2,5,6} The prognosis of these patients is quite unfavourable due, mainly to the fact that diagnosis is established in an advanced stage of the disease.^{2,6}

The aim of our study is to determine the incidence of BC in our hospital's transplant patients and the role of surgery.

Patients and method

Until December 2006, in the Hospital Universitario La Fe, 3596 patients have undergone solid organ transplants and 24 (0.7%) patients subsequently developed BC. The incidence rate, according to type of transplant, was 10 out of 1539 (0.6%) subject to kidney transplant, 9 out of 1249 (0.7%) liver transplants, 4 out of 498 (0.8%) heart transplants, and 1 out of 311 (0.3%) lung transplants. Six patients (24%) were classified

as clinical stage I and they were submitted to surgical treatment. Four patients were rejected for surgery based on functional criteria and 14 due to oncological criteria (4 with microcytic carcinoma, 5 in stage IIIB, and 7 in stage IV).

Preoperative assessment included: general clinical state—Eastern Cooperative Oncology Group (ECOG)—, haemogram, basic biochemistry, coagulation, electrocardiogram (ECG), spirometry, thoracoabdominal and cerebral computerised tomography (CT), and positron emission tomography (PET). The diagnosis of BC was established before surgery via fibrobronchoscopy or transparietal puncture. Death from BC or another cause was the terminal event for survival calculation, estimated using the Kaplan-Meier method. Observation date was established as May 1, 2008.

Results

The clinical, surgical, histological, and evolution characteristics are detailed in Tables 1 and 2. All male, with an average age of 58.6 (range, 47-66). They all had an over 30 year history of smoking one packet/day. There were 3 former smokers and 3 active smokers at the time of BC diagnosis; 2 patients had a cough, 1 accompanied by blood expectoration and the BC was an incidental finding in the remaining cases; 3 had undergone liver transplants; 2 had kidney transplants and 1 had a heart transplant. The interval between the transplant and BC diagnosis was 38.2 (range, 13-61) months. A pneumonectomy,

Table 1 – Demographic and clinical features

Case	Age	Smoker	Symptoms	Transplant	Range, ^a mo
1	52	Former smoker	Cough	Heart	61
2	47	Former smoker	Blood expectoration	Liver	44
3	60	Smoker	Asymptomatic	Liver	13
4	62	Former smoker	Asymptomatic	Kidney	32
5	65	Smoker	Asymptomatic	Liver	31
6	66	Smoker	Asymptomatic	Kidney	48

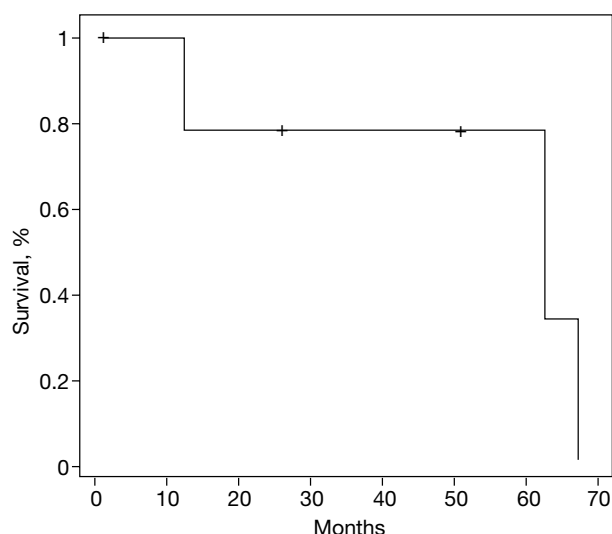
All the patients were male.

^aInterval between the transplant and development of the bronchogenic carcinoma.

Table 2 – Intervention, tumour type, size, TNM, and survival

Case	Intervention	Type	Size, cm	Pathological TNM	State	Survival, mo
1	Lobectomy	Epidermoid carcinoma	6	T2N0M0	Deceased	65
2	Pneumonectomy	Epidermoid carcinoma	4.5	T2N0M0	Deceased	61
3	Wedge	Adenocarcinoma	4	T2N0M0	Living	50
4	Lobectomy	Epidermoid carcinoma	1.5	T1N0M0	Deceased	15
5	Lobectomy	Epidermoid carcinoma	4.5	T3N0M0	Living	27
6	Wedge	BAC	1.3	T2N0M0	Living	5

BAC indicates bronchioloalveolar carcinoma.

**Figure – General patient survival.**

3 lobectomies, and 2 wedge resections were performed. The most frequent histological type was the epidermoid carcinoma. The average tumour size was 3.6 (range, 1.3-6) cm. One tumour was classified as pathological stage IA, 4 as stage IB and 1 as IIB due to parietal pleural invasion.

No patient died during the perioperative period and only 1 had a haemothorax which was resolved with intrathoracic

drainage. The average hospital stay was 8.5 (range, 7-11) days. The immunosuppression regimen was maintained continuously. In subsequent follow-up, 1 patient died from BC metastasis, 1 from sepsis, 1 from chronic renal failure, and 3 remained alive. The probability of survival at 5 years was 40%, and median survival was established at 5 years (Figure).

Discussion

Certain carcinomas frequently observed in the population, such as squamous cell carcinoma or carcinoma in situ of the uterine cervix; present a significantly higher incidence rate in the transplanted segment. By contrast, in other carcinomas, including BC, there is no evidence of this.¹ Certain authors have not substantiated a greater incidence of BC in transplant patients with respect to the general population.^{2,5,6} In our experience, although the BC rate was relatively low (0.7%), it was higher than that observed in our institution in non-transplant patients (0.05%-0.1%).⁷ In the past decade, some authors have observed a high rate of BC in patients subject to heart transplants.^{3,4} However, we agree with other authors in that there is no relation between suffering BC and the type of transplant undertaken, but it is related to a previous history of smoking.²

It has been confirmed in previous check-ups that, approximately 90% of the transplant patients that then manifested BC were or had been smokers, the majority were

male and the average age was 50-60.^{2,5,6} These observations coincide with our experience and bring into relief that there are no differences in the appearance of BC in the transplanted population with regards to the general population. This could question the role of immunosuppression treatment as a main aetiological factor, especially keeping in mind that when a BC has been observed in lung transplant patients, it was in single lung transplants and the tumour, as occurred in our study, was on the recipient's native lung. Ahmed et al,⁸ in a series of patients subject to surgery with results, in terms of survival, similar to our series, consider that while smoking is the main risk factor, immunosuppression seems to also play an important role, especially in transplant patients followed-up in the long term. This is the case of kidney transplant patients, in which the incidence of BC also seems to have increased even without a background of smoking. In this sense, Bellil et al,⁹ also comment on the increase in the BC incidence rate in transplant patients, in which smoking is once again the key risk factor; even though immunosuppression could condition both the incidence increase and the tumour aggression at the time of diagnosis.

When the BC diagnosis is established, the tumour is in an advanced stage in approximately two thirds of the patients, so very few patients are surgically treated.² This observation could be the consequence of the effect of immunosuppression treatment in tumour growth and spreading, as has been experimentally proven.¹⁰ On the other hand, the diagnostic confusion of labelling a BC as an infection is not infrequent.^{11,12} In a recent review, Bagan et al⁶ substantiated that 38% of heart transplant patients that later developed BC underwent complete surgery. In our experience, the rate of patients classified at clinical stage I (25%) is not significantly lower than observed in our institution,⁷ which also questions the role of immunosuppression in tumour aggression.

The survival average in patients subject to curative surgery is in the region of 23 months, conditioned by the pathological state and the comorbidity of the transplant patient and also conditions the perioperative morbidity and mortality.⁶ The survival average in our study was 60 months, with acceptable morbidity without perioperative mortality.

To conclude, in our experience, BC incidence in patients subject to solid organ transplant is slightly higher than in the non-transplanted population. However, the rate of patients diagnosed in early stages and who could benefit from surgical treatment does not differ from that of non-transplant patients.

Finally, surgery can offer acceptable results in early stages, with satisfactory perioperative morbidity and mortality.

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