23. Mason BH, Holdaway IM, Mullins PR, Yee LH, Kay RG. Progesterone and estrogen receptors as prognostic variables in breast cancer. *Cancer Res* 1983, **43**, 2985–2990.
24. McCarty KS, Barton TK, Fetter BF, *et al.* Correlation of estrogen and progesterone receptors with histologic differentiation in mammary carcinoma. *Cancer* 1980, **46**, 2851–2858.
25. Mohammed RH, Lakatua DJ, Haus E, Yasmineh WJ. Estrogen and progesterone receptors in human breast cancer. Correlation with histologic subtype and degree of differentiation. *Cancer* 1986, **58**, 1076–1081.
26. Coulson PB, Thornthwaite JT, Woolley TW, Sugarbaker EV, Seckinger D. Prognostic indicators including DNA histogram type, receptor concent, and staging related to human breast cancer patient survival. *Cancer Res* 1984, **44**, 4187–4196.
27. Vollmer G, Gerdes J, Knuppen R. Relationship of cytosolic estrogen and progesterone receptor content and the growth fraction in human mammary carcinomas. *Cancer Res* 1989, **49**, 4011–4014.
28. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987, **235**, 177–182.
29. Delaure JC, Friedman S, Mouriesse H, *et al.* Epidermal growth factor receptor in human breast cancers: correlation with estrogen and progesterone receptors. *Breast Cancer Res Treat* 1988, **11**, 173–178.
30. Simpson HW, Pauson AW, Griffiths K, Candlish W, McArdle CS, Small RG. Genesis of breast cancer in the premenopause. *Lancet* 1988, i, 74–76.

Acknowledgement—This work has been supported by Research Council of SR Croatia grant No. 1. 04.01.01.103.

Eur J Cancer, Vol. 27, No. 4, pp. 495–498, 1991.
Printed in Great Britain

0277-5379/91 $3.00 + 0.00

Pulmonary Tumour Embolism from Squamous Cell Carcinoma of the Oesophagus

Fernando A. Soares, Glaucia A. Magnani Landell and Jose A. Mello de Oliveira

Pulmonary tumour embolism and subacute "cor pulmonale" have been reported in association with tumours of different origins. Even though these features were first described in a patient with carcinoma of the oesophagus, the frequency and importance of oesophageal tumours as the source of pulmonary tumour embolism have not been studied. In the present investigation, the lungs of 16 autopsied patients with squamous cell carcinoma of the oesophagus were studied prospectively. The lungs were removed as a block and 15 sections (3 from each lobe) were analysed. Pulmonary tumour embolism was detected in 7 cases. The lymphatic vessels were involved in all of them, and were associated with arteries and arterioles in 2. 2 patients presented a classical picture of subacute cor pulmonale, and dyspnoea was present in 3 other cases. The present study permitted us to conclude that carcinomas of the oesophagus frequently evolve toward carcinomatous lymphangitis and that pulmonary tumour embolism should be included in the differential diagnosis of the dyspnoea presented by the patients.
Eur J Cancer, Vol. 27, No. 4, pp. 495–498, 1991

INTRODUCTION

PULMONARY TUMOUR embolism was first described in 1868 by Bristowe, who reported the development of secondary pulmonary arterial hypertension in a patient with carcinoma of the oesophagus [1]. The author correlated the clinical picture with the presence of intense carcinomatous lymphangitis. In 1937, Brill and Robertson developed the concept of subacute cor pulmonale as an entity characterised by the rapid development of symptoms of right congestive heart failure in patients with no previous history of cardiopulmonary disease or other conditions triggering right ventricular failure [2]. Several studies of pulmonary vessel involvement secondary to tumours have been conducted over the years, including large series in retrospective studies [3–6].

With respect to the primary tumour sites that most frequently cause the involvement of lymphatic and blood vessels of the lung, the literature always placed strong emphasis on the stomach [3, 4, 7–12]. Other organs have also been indicated, such as the breast [3, 6, 13, 14], the lung itself [5], the liver [3, 15, 16] and the kidney [3, 6, 17]. Isolated cases of development of subacute cor pulmonale from tumours originating in practically all body organs have been reported. To our knowledge, no studies or even case reports of pulmonary vascular involvement in carcinoma of the oesophagus have been published.

For this reason, in the present investigation we studied prospectively 16 consecutive autopsies of patients with primary squamous cell carcinoma of the oesophagus in terms of the development of pulmonary tumour embolism and its clinicopathological manifestations.

MATERIAL AND METHODS

Pulmonary vessel tumour involvement was studied in 16 consecutive autopsies performed between 1986 to 1989 in patients with squamous cell carcinoma of the oesophagus in the Department of Pathology, Faculty of Medicine of Ribeirão Preto, University of São Paulo.

Clinical data concerning the presence or absence of dyspnoea, cyanosis and right congestive heart failure and the modality of treatment were obtained from medical records of the patients.

Correspondence to F.A. Soares.
The authors are at the Department of Pathology, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Av. Bandeirantes 3900, 14049 Ribeirão Preto SP, Brazil.
Revised 30 Nov. 1990; accepted 25 Jan. 1991.

Table 1. *Summary of* 16 *cases studied*

Case	Vessel involvement	RVF	Dyspnoea	RVH	VS	Metastasis	Stage of disease	Main cause of death
1	–	–	+	–	–	None	III	Oesophagobronchial fistulae
2	Lymphatics	–	–	–	–	Lymph nodes	III	Diffuse alveolar damage
3	Lymphatics Muscular arteries Arterioles	–	–	–	–	Liver, lungs Lymph nodes	IV	Oesophagobronchial fistulae
4	–	–	–	–	–	Lymph nodes	III	Oesophagobronchial fistulae
5	Lymphatics	–	–	–	–	Lymph nodes	IV	Oesophagobronchial fistulae
6	Lymphatics	+	+	+	+	Liver Lymph nodes	IV	Subacute cor pulmonale
7	–	–	–	–	–	Lymph nodes	III	Oesophagobronchial fistulae
8	–	–	–	–	–	Liver	IV	Meningitis
9	Lymphatics	–	+	–	–	None	III	Oesophagobronchial fistulae
10	–	–	–	–	–	None	II-A	Acute peritonitis
11	–	–	–	–	–	None	III	Oesophagobronchial fistulae
12	–	–	–	–	–	None	III	Pulmonary embolism
13	–	–	–	–	–	None	III	Oesophagobronchial fistulae
14	Lymphatics Muscular arteries Arterioles	+	+	+	+	Lymph nodes, Lungs	IV	Subacute cor pulmonale
15	–	–	+	–	–	None	III	Oesophagobronchial fistulae
16	Lymphatics Muscular arteries Arterioles	–	–	–	–	Lymph nodes	III	Digestive bleeding

RVF = right ventricular failure, RVH = right ventricular hypertrophy, VS = vascular sclerosis.

Data about right ventricle thickness and analysis of metastatic sites were recorded at autopsy. The stage of the disease according to UICC [18] was carefully recorded in each case.

The lungs were removed as a block and injected through the trachea with sufficient formalin to obtain good expansion of the organ. After fixation, 15 lung tissue fragments (3 from each pulmonary lobe) were obtained, embedded in paraffin and submitted to routine histological processing. Sections were stained with haematoxylin–eosin. Material in which tumour cells were present in the pulmonary vessels were also stained by the Verhoeff method.

Histological examination was based on the determination of the type of pulmonary vessels involved and of the vascular changes caused by the possible increase in pulmonary arterial pressure. Other histopathological features of the lungs were also recorded.

RESULTS

The results are summarised in Table 1. Pulmonary vascular involvement was observed in 7 cases. All of them presented carcinomatous lymphangitis (Fig. 1). and 3 also showed involvement of muscular arteries and arterioles (Fig. 2).

2 patients had developed clear signs and symptoms of right heart failure, and 2 of the 5 patients with pulmonary vascular involvement presented dyspnoea of no other aetiological cause. 2 of the patients without pulmonary tumour embolism had presented dyspnoea, 1 caused by tracheal compression consequent to the large tumour mass and other by oesophagobronchial fistulae and bronchopneumonia. Cyanosis was not observed in any of the patients. Only 5 patients had been treated previously, 3 of them (cases 2, 4 and 5) with radiotherapy and 2 (cases 9 and 12) with surgery. All other patients had received only palliative treatment with gastrostomy or transtumoral intubation.

2 patients (cases 6 and 14) had presented right ventricular hypertrophy which was associated with signs of pulmonary vascular sclerosis (Fig. 3).

With respect to stage of disease at death, patients were either in stage III (cases 1, 2, 4, 7, 9, 11, 12, 15 and 16) or stage IV (cases 3, 5, 8 and 14), and in only 1 patient (case 10) was the tumour restricted to the organ. In regard to metastatic sites, we emphasise case 9 in which the tumour was localised with involvement of the subpleural lymphatic vessels.

Pulmonary tumour embolism and subacute cor pulmonale were considered to be the main cause of death for 2 patients (cases 6 and 14) and as factors contributing to the cause of death for 3 other patients (cases 3, 9 and 16). The main cause of death for the remaining patients was oesophagobronchial fistulae–bronchopneumonia in 9 cases, diffuse alveolar damage in 1,

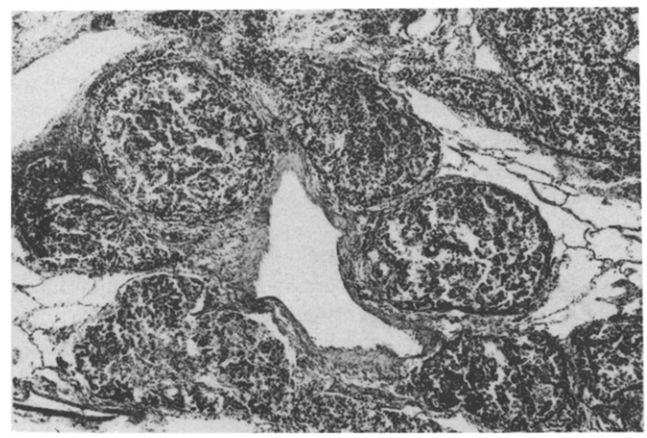

Fig. 1. Nests of neoplastic cells in perivascular lymphatics of the lung (× 40).

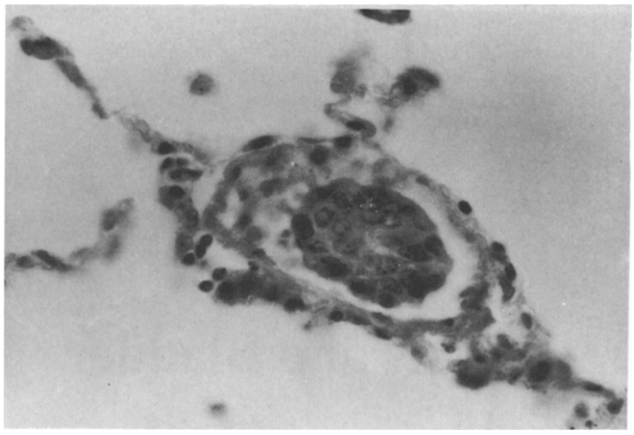

Fig. 2. Pulmonary arteriole showing intraluminal tumour cells (× 280).

purulent meningitis in 1, acute peritonitis in 1, pulmonary embolism in 1 and digestive bleeding in 1.

DISCUSSION

Squamous cell carcinoma of the oesophagus is a common neoplasm of the digestive tract accounting for 3.4% of all malignant tumours in Brazil [19]. Metastatic spread to the lungs occurs in 15–52% of cases and is an important cause of death [20–21].

Pulmonary tumour embolism has been recognised in neoplasms from the most diverse primary sites [3–6] with the stomach being the organ most frequently affected [3, 4, 7, 8–12]. Even though the oesophagus was the primary site in the case for which the entity was first reported, no cases of pulmonary tumour embolism, with or without the development of subacute cor pulmonale, have been reported to originate from squamous cell carcinomas of the oesophagus. There are no studies of the behaviour of carcinomas of the oesophagus in relation to pulmonary vessel involvement. Only Chomette *et al.* referred to a study of 76 cases of oesophageal tumours [6]. The authors included these cases in the group of other primary sites without any special emphasis, thus preventing an appropriate analysis of the results in relation to the organ. The present study demonstrates that the oesophagus can be a frequent source of pulmonary embolism, usually in association with disease in the advanced stage, with metastatic spread to thoracic lymph-nodes and to distant sites. Carcinomatous lymphangitis are usually detected but tumoral cells can be detected also in blood vessels. This may occur in situations of localised disease, and recognising this occurrence is important for patient management.

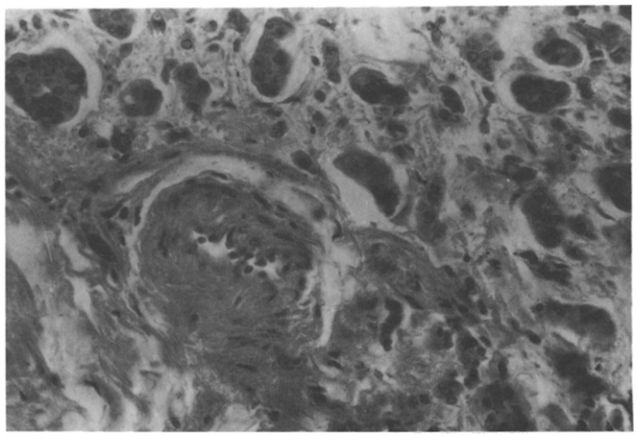

Fig. 3. Pulmonary arteries with marked fibrosis of the media and perivascular lymphangitis carcinomatosis (× 200).

Pulmonary hypertension is a rare complication of tumoral lung involvement. Subacute cor pulmonale is a well known entity which, however, is still of doubtful aetiopathogenesis. Some investigators believe that vascular sclerosis of pulmonary arteries is associated with the presence of tumour cells in the lumen of arterioles which occlude the circulation and function in a manner analogous to that of pulmonary microembolism [4, 5]. However, theories such as extrinsic compression of blood vessels by distended lymphatic vessels or invasion of vascular walls by neoplastic cells are other mechanisms that have been proposed [2, 12]. Two cases of classical subacute cor pulmonale was observed in the present sample (cases 6 and 14).

Patients with cancer of the oesophagus who develop dyspnoea are almost always considered to have developed pulmonary metastases or oesophagobronchial fistulae. In the present sample, in 3 cases with pulmonary tumour embolism in which dyspnoea had occurred, we did not observe involvement of the lung parenchyma by the tumour or by an inflammatory process. In our opinion, pulmonary tumour embolism should be included in the differential diagnosis of dyspnoea in patients with squamous cell carcinoma of the oesophagus.

1. Bristowe JS. Colloid cancer of oesophagus, stomach, lungs and adjoining lymphatic glands. *Trans Path Soc* 1868, **19**, 228–236.
2. Brill IC, Robertson TD. Subacute cor pulmonale. *Arch Intern Med* 1937, **60**, 1043–1057.
3. Winterbauer RH, Elfenbein IB, Ball WC Jr. Incidence and clinical significance of tumor embolization to the lungs. *Am J Med* 1968, **45**, 271–290.
4. Kane, RD, Hawkins HK, Miller JA, Noce PS. Microscopic pulmonary tumor emboli associated with dyspnea. *Cancer* 1975, **36**, 1473–1482.
5. Gonzalez-Vitale JC, Garcia-Bunuel R. Pulmonary tumor emboli and cor pulmonale in primary carcinoma of the lung. *Cancer* 1979, **38**, 2105–2110.
6. Chomette G, Auriol M, Sevestre C, Acar J. Les embolies pulmonaires néoplasiques. Expressions cliniques et incidence anatomique. *Ann Méd Interne* 1980, **131**, 217–221.
7. Wu TT. Generalised lymphatic carcinosis ("Lymphangitis carcinomatosa") of the lungs. *J Path Bact* 1936, **43**, 61–76.
8. Kupari M, Laitinen L, Hekali P, Luomanmäki K. Cor pulmonale due to tumor cell embolization. Report of a case and a brief review of the literature. *Acta Med Scand* 1981, **210**, 507–510.
9. Tesar PJ, Goy J, Maynard J. Lymphangitis carcinomatosa. *Med J Aust* 1981, **1**, 80–81.
10. Dennstedt FE, Greenberg SD, Kim H-S, Weilbaecher DG, Bloom K. Pulmonary lymphangitic carcinomatosis from occult stomach carcinoma in young adults. An unusual cause of dyspnea. *Chest* 1983, **84**, 787–788.
11. Rellini G, Charmet PP, Burelli C, *et al.* Carcinomatosi polmonare: causa inusuale di cuore polmonare acuto. *G Ital Cardiol* 1986, **16**, 479–486.
12. Aiello VD, Mansur AJ, Lopes EA, Bellotti G, Pillegi F. Severe pulmonary hypertension due to carcinomatous lymphangitis of the lungs associated with unsuspected gastric cancer. *Am Heart J* 1988, **116**, 197–198.
13. Durham JR, Ashley PF, Dorencamp, D. Cor pulmonale due to tumor emboli. *JAMA* 1961, **175**, 757–760.
14. Fanta CH, Compton CC. Microscopic tumor emboli to the lungs: a hidden cause of dyspnoea and pulmonary hypertension. *Thorax* 1979, **43**, 794–795.
15. Brisbane JU, Howell DA, Bonkowsky, HL. Pulmonary hypertension as a presentation of hepatocarcinoma. Report of a case and brief review of the literature. *Am J Med* 1980, **68**, 466–469.

16. Willett IR, Sutherland RC, O'Rourke MF, Dudley FJ. Pulmonary hypertension complicating hepatocellular carcinoma. *Gastroenterology* 1984, **87**, 1180–1184.
17. Novick AC, Daughtry JD, Stewart BH, Graves LR. Pulmonary embolus presenting as initial manifestation of renal cell carcinoma. *Urology* 1978, **12**, 707–709.
18. Hermanek P, Sobin LH, eds. *TNM. Classification of malignant tumors*, 4th ed. Berlin, Springer, 1987, 40–42.
19. Brumini R, ed. *Cancer in Brazil. Histopathological data 1976–1980*. Rio de Janeiro, Ministério de Saude, 1982.
20. Anderson LL, Lad TE, Autopsy findings in squamous cell carcinoma of the esophagus. *Cancer* 1982, **50**, 1587–1590.
21. Raven RW. Carcinoma of esophagus: a clinicopathologic study. *Br J Surg* 1948, **36**, 70–73.

Acknowledgement—The authors thank Mr Jose Luiz de Souza and Mrs Tereza C. Pantozzi Silveira for their technical assistance.

Eur J Cancer, Vol. 27, No. 4, pp. 498–500, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Urinary Infection, Renal Lithiasis and Bladder Cancer in Spain

Carlos A. González, Manuel Errezola, Isabel Izarzugaza, Gonzalo López-Abente, Antonio Escolar, Manuel Nebot and Elio Riboli

A case-control study on bladder cancer was carried out in 12 hospitals located in 4 regions of Spain. The study included 497 cases and 530 population controls, matched by sex, age and residence. The present paper reports the results regarding the risk for bladder cancer in relation to history of infections and lithiasis of the urinary tract. Increased risk was found for infections starting 4 years or less before diagnosis (OR = 15.00; 95% CL: 6.07–51.66) but no statistically significant increase in risk was observed for infections starting 5 or more years before (OR = 1.44; 95% CL: 0.86–2.47). Our data suggest that the association of urinary infections with bladder cancer is probably not causal and is more likely to be a consequence of cancer, although a weak causal association cannot be excluded. A small but not statistically significant increase in risk was found to be associated with a history of renal lithiasis.
Eur J Cancer, Vol. 27, No. 4, pp. 498–500, 1991

INTRODUCTION

THE ASSOCIATION between a history of urinary infection and bladder cancer is controversial. Hospital based case-control studies [1–3] and population based studies [4] have shown an increased risk, but they did not take into account the period between onset of infection and appearance of the tumour. On the other hand, in a case-control study for which this information was available [5], the relative risk for infections of the bladder occurring during the 5-year period prior to diagnosis was 4.9 in males and 2.8 in females, but no increase in risk was reported for infections which started more than 5 years prior to diagnosis. Neither was any increased risk observed in a recent study on women which considered infections occurring at least 2 years prior to diagnosis [6].

There is, however, evidence to support the possibility of an association with urinary infection, particularly in cases of squamous cell carcinoma. An increase in these tumours has been described, associated with chronic urinary infections [7] and in areas of endemic schistosomiasis [8].

Two possible causal pathways of the infections have been suggested: one directly through bacterial flora which would favour the formation of nitrosamines from precursors such as nitrites and nitrates [9] and the other indirectly, in that the infection would increase absorption and/or exposure to carcinogens in the urine. An alternative explanation is that there may be no causal association, simply that the infection may be a consequence of the development of the tumour itself [5].

The other major disease of the urinary tract which has been considered as a potential risk factor for bladder cancer is urinary lithiasis [4, 5]. Increased risk has been reported for patients with a history of urinary bladder lithiasis but no history of urinary infection [5]. On the other hand, no increased risk in relation to renal lithiasis was observed.

In the present paper we present the results, with respect to histories of urinary infection and renal lithiasis, of a multicentre case-control study carried out in Spain. The study also investigated the risk associated with active and passive consumption of tobacco (G.L.-A. *et al.*), job exposure [10], diet (E.R. *et al.*) and consumption of coffee and artificial sweeteners.

MATERIALS AND METHODS

The study was carried out in 1985 and 1986 in the provinces of Barcelona, Madrid, Cadiz, Guipuzcoa and Biscay. Recruitment of cases was based on the registers of 12 hospitals belonging to or associated with the Social Security System, which cover

Correspondence to E. Riboli.
C.A. González is at the Epidemiological Unit, Hospital Sant Jaume i Sta Magdalena, Barcelona; M. Errozola is at the Department of Health and Social Security, Basque Government, Vitoria; G. López-Abente is at the Health Research Fund (FISS), Madrid; A. Escolar is at the Provincial Delegation, Health and Consumer Council, Cadiz; M. Nebot is at the Municipal Health Institute, Barcelona Town Hall, Spain; and E. Riboli is at the International Agency for Research on Cancer (IARC), 150 cours Albert-Thomas, 69372 Lyon Cédex, France.
Revised 21 Dec. 1990; accepted 4 Jan. 1991.