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Pleural metastatic tumours and effusions. Frequency and pathogenic mechanisms in a post-mortem series

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Pleural metastatic tumours and effusions. Frequency and pathogenic mechanisms in a post-mortem series. F. Rodrîguez-Panadero, F. Borderas Naranjo, J. López Mejîas.

ABSTRACT: We examined the post-mortem records of 191 patients who had one or more malignant tumours (196 neoplasms in total). We found 55 cases with pleural metastases (28%) and 30 of these presented pleural effusions (15% of the total number of neoplasms). The visceral pleura was involved in all 24 cases of lung cancer with pleural metastasis and in 27 out of 31 of those of other origins. The parietal pleura was affected in 16 out of 24 cases of the lung tumours and in 15 out of 31 of those of other origins. There were no cases in which only the parietal layer of the pleura was involved, with the only exception of neighbouring tumours. We found neoplastic vascular invasion in 43 out of 55 cases, retrograde lymphatic spread from the mediastinum in two cases, and direct pleural involvement from a neighbouring tumour in the remaining. We conclude that malignant pleural implantation fundamentally arises from the spread of tumour emboli to the lungs and the visceral pleura, with secondary seedings to the parietal pleura. Therefore, this phenomenon leads to the usual finding of lower involvement of parietal pleura as compared to the visceral pleura in our series.

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The finding of a pleural effusion in a patient with a known tumour is considered an ominous sign. Nevertheless, there is still a lack of certainty as to the prevalence of pleural metastases in malignant neoplasms, the proportion of cases with pleural metastases that develop effusions, and the pathogenesis of the metastases implanted in the pleural layers.

MEYER [1] established several facts that related to these questions, such as: pleural metastases do not precisely coincide with effusions of the same location, the importance of lymphatic blockade at the mediastinal level, and the role that arterial emboli play in the genesis of pleural metastases arising from bronchial carcinoma. He established also that hepatic metastases are usually involved in the spread of extrapulmonary tumours to the pleura, except in the case of neoplasms of the thoracic wall.

Based on a revision of post-mortem records, we investigated the role lymphatic blockade played in bringing about pleural effusions [2] and our results were in agreement with those of MEYER [1]. In the present paper we investigated the frequency of pleural metastases in patients with malignant tumours, the implantation and distribution mechanisms of tumour metastases that affect the pleura, and their relation to effusions.

Patients and methods

We reviewed the records of the necropsies carried out at our hospital during the past 18 yrs (22% of all deaths), and found 196 cases of malignant neoplasms in 191 patients. All the autopsies were done by well trained members of the staff of the Department of Pathology. The following data and findings were recorded systematically:

1. external appearance, body weight and height;
2. upper and lower airways;
3. pleural cavities, with references to findings in pleura at visceral, parietal, diaphragmatic and mediastinal surfaces. We performed microscopic studies on each pleural surface only when macroscopically visible lesions were found;
4. mediastinum;
5. lungs, with references to weight, external appearance and findings after systematic cuttings;
6. heart and pericardium;
7. abdominal cavity, with references to findings in peritoneum, liver, spleen, pancreas, abdominal surface of diaphragm, intestine, colon, kidneys, adrenal glands and genito-urinary tract;
8. spine;
9. we systematically studied in every case, both microscopically and macroscopically, the vascular invasion in the primary tumour site, in the metastases and in the pulmonary circulation.

The 191 neoplasm cases were studied for possible occurrence of pleural metastases, and these were found in 55 cases. This group of 55 cases was then investigated for the origin of the neoplasms, their histological types, as well as for tumour involvement of the adjacent lung,

lymphatic mediastinal involvement, uni- or bi-lateral pleural effusion, and tumour affection in the liver, peritoneum, pancreas, kidneys, adrenals and other organs. We especially looked for tumour invasion into the vascular system at the pulmonary level, or at the level of the viscera from which the tumour had arisen or metastasized.

The pleural affection was studied to ascertain if there had been direct invasion from a neighbouring tumour, diffuse or isolated metastasis, and to determine in which pleural zones - visceral, costal, diaphragmatic or mediastinal - it had been found.

We used the chi-squared and exact Fisher's test for the statistical study.

Results

The total number of neoplasms with and without pleural involvement, and the histologic classification, are specified in table 1. Pleural involvement was found in 55 of the 191 cases of malignant neoplasms, and malignant pleural effusions were found in 30 of these 55 cases (15% of the total number of neoplasms).

The scarcity of breast tumour in our series is due to the fact that we perform very few necropsy studies in this tumour group, since the diagnosis is already made during the patient's life.

The effusion was bilateral in 14 out of 30 cases, left-sided in 9 and right-sided in 7. There were six patients with metastatic pleural effusion in one side and non-metastatic effusion in the other, and in five of these six cases we found mediastinal lymphatic blockade.

The distribution of the pleural metastases is outlined in table 2. The pleural metastases of the primary pulmonary tumours were exclusively ipsilateral in 17 of the 24 cases. They were unilateral only in 12 out of 31 cases of other origins ($p<0.04$). It was especially interesting, that at no time was the parietal layer of the pleura exclusively involved, with the exception of cases of neighbouring tumours. Whenever the parietal layer was affected, it was always accompanied by metastases of the visceral pleura of the same side.

Hepatic metastases were recorded in half of the neoplasms that originated in the lungs and 71% of those of other origins.

In table 3 the mechanisms of pleural involvement are classified into two groups: a) direct invasion from a

Table 1. – Metastatic pleural involvement and histological types

Origin	Pleural metastasis n	Pleural effusion n
Lung {n=39}*		
Squamous cell carcinoma	5	3
Small cell carcinoma	7	5
Adenocarcinoma	8	6
Large-cell carcinoma	3	1
Mucoepidermoid carcinoma	1	–
Lymphoma - Leukaemia {n=28}*		
Hodgkin	2	1
Non Hodgkin	5	4
Others {n=129}*		
Adenocarcinoma of (total)	18	
Liver	4	1
Gall bladder	3	1
Kidney	3	2
Colon	2	1
Pancreas	1	–
Thyroid gland	2	1
Bladder	1	1
Salivary glands	1	–
Breast	1	1
Sarcoma (total)	3	
Thoracic wall	1	1
Diaphragm	1	–
Breast	1	–
Epidermoid carcinoma of the thymus	1	–
Oat-cell carcinoma of the pancreas	1	–
Myeloma	1	1
Total: 196 neoplasms**	55 (28%)***	30 (15%)***

* We quote within { } the total tumour number in each group in our necropsy series; **: we found 196 malignant tumours in 191 patients; ***: the percentages in these columns are calculated on the total tumour number.

neighbouring tumour, and b) vascular invasion detectable macroscopically as pulmonary arterial tumour emboli or as microscopic vascular invasion at the level of the primary tumour. In 32 of the 55 cases tumour vascular invasion (permeation) was found. Macroscopic tumour emboli were found in 3 of the 24 cases of lung cancer. In distant extrapulmonary tumours with pleural metastases but without hepatic involvement, vascular permeation was always detected at the level of the primary tumour, along with pulmonary metastases that rendered evidence of neoplastic cell embolization.

Table 2. – Distribution of neoplastic lesions in the pleura

	Origin of the tumour	
	Lung (n=24)	Other (n=31)
Visceral pleura (9)*		
Unilateral	17	10
Bilateral	7	17
Costal pleura (0)**		
Unilateral	13	9
Bilateral	3	6
Diaphragmatic pleura (3)***		
Unilateral	7	9
Bilateral	1	8
Mediastinal pleura (1)****	15	7

Notes: *: we quote within ( ) the cases in which there was exclusive pleural involvement in this zone; **: in 24 out of 55 pleural tumours there was no costal pleural involvement (the zone that is accessible by blind needle biopsy). There was always adjacent visceral pleural involvement when the parietal pleura was involved, with the exception of primary chest wall or mediastinal tumours; ***: exclusive diaphragmatic involvement was found only in two cases of primary tumour of the liver and in one case of lymphoma; ****: exclusive mediastinal pleural involvement was seen only in one case of lymphoma.

Direct pleural invasion from the mediastinum was frequently found in lymphomas. Several metastatic mechanisms often coexisted in the same patient, but it was truly exceptional to find data on a retrograde lymphatic spread from the mediastinum to the pleura, (table 3).

Discussion

Our most important finding is that the parietal pleura is less frequently involved than the visceral pleura in the metastatic process. This was true not only in cases of bronchopulmonary cancer but in those of extrapulmonary origin as well, and could explain the better results of thoracoscopic biopsy as compared with needle "blind" biopsy of the parietal pleura [3, 4].

At no time was the parietal layer of the pleura exclusively involved. The only exceptions to this rule were the tumours of the thoracic wall which directly reached the parietal pleura. This indicates that the tumour cells will first spread to the visceral pleura from the lungs and then produce neoplastic implants: these would cast off cells to the pleural cavity which would then give rise to secondary implants in the parietal pleura and diaphragm. This "sedimentary" mechanism of pleural metastasis was invoked by WILLIS [5] and is supported by the common finding of a greater accumulation of neoplastic lesions on the lower zones of the pleural cavity, both at visceral and parietal level [5–7].

According to MEYER [1] and WILLIS [5] the 'primary' implants in the visceral pleura do not necessarily have to be very large except in the case of lung tumours which grow right into it. This could explain the slightly higher frequency of grossly visible metastatic findings in parietal than in visceral pleura in some thoracoscopic series concerning tumours of extrapulmonary origin [7, 8]. However, in cases of lung cancer there is always a higher frequency of metastatic lesions found in visceral pleura [8]. Further prospective necropsy studies are needed with systematic microscopic examinations of both parietal and visceral pleura, regardless of the macroscopic appearance.

MEYER [1] attributed the ipsilateral pleural metastases in lung cancers to pulmonary arterial embolization, and in agreement with this we have found pulmonary vascular invasion by the tumour in 19 of our 24 pulmonary cases (table 3). We also came across this same tumour embolization phenomenon in neoplasms of other locations. These findings agree with those of MORGAN [9] as well as those of JANOWER and BLENNER HASSETT [10] among others.

The primary interest in MEYER's study [1] was placed on the role that hepatic metastases played in the genesis

Table 3. – Mechanisms by which tumours spread to the pleura

Origin (n)	Direct	Vascular invasion		Others
		Tumour embolism	Microscopic	
Lung (24)	7*	3	16	–
Lymphoma-leukaemia (7)	3*	1	3**	1***
Others (24)	8*	7	13	1****
Totals	18 (33%)	11 (20%)	32 (58%)	2 (4%)

Notes: *: the neoplasms in which several dissemination mechanisms were observed in some cases are indicated; **: in one of these cases, both hepatic vascular permeation and pulmonary tumour embolism were found; *** in this case a retrograde lymphatic spread from the mediastinum is suggested; **** in this case (tumour of the salivary glands) a lymphatic spread through the mediastinum is suggested.

of pleural seeding by extrathoracic tumours. These were encountered only in 71% of our cases. This means that such metastatic involvement can be absent even in advanced neoplasms and that it is not indispensable for pleural dissemination to arise. Vascular tumour permeation - which in addition to the liver, can be associated with any other organ - is certainly fundamental for this seeding to come about.

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Tumeurs et épanchements pleuraux métastatiques. Fréquence et mécanismes pathogéniques dans une statistique post-mortem. F. Rodríguez-Panadero, F. Borderas Naranjo, J. López Mejías.

RÉSUMÉ: Nous avons examiné les comptes rendus post-mortem de 191 patients qui avaient une ou plusieurs tumeurs malignes (au total, 196 néoplasmes). Nous avons trouvé 55 cas avec métastases pleurales (28%) et 30 de ceux-ci avaient des épanchements pleuraux (15% du nombre total de néoplasmes). La plèvre viscérale était entreprise dans la totalité des 24 cas de cancer du poumon avec métastases pleurales, et dans 27 de 31 autres cancers. La plèvre pariétale était atteinte dans 16 des 24 cas de tumeurs pulmonaires et dans 15 des 31 métastases d'autres origines. On n'a pas trouvé de cas où seule la plèvre pariétale était entreprise, à l'exception des tumeurs de voisinage. Nous avons trouvé un envahissement vasculaire néoplasique dans 43 des 55 cas, une dissémination lymphatique rétrograde à partir du médiastin dans deux cas, et une atteinte pleurale directe provenant d'une tumeur voisine dans les autres. Nous concluons que l'implantation pleurale maligne provient essentiellement de la dispersion d'embolies tumorales aux poumons et à la plèvre viscérale, avec envahissement secondaire de la plèvre pariétale. Ceci en responsable d'une atteinte moins fréquente de la plèvre pariétale par comparaison avec la plèvre viscérale dans notre série.

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