The Pleural Form of Primary Cancer of the Lung

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Primary cancer of the lung in its usual anatomical manifestations assumes different formal aspects on which clinical characteristics of its progress and development largely depend.

In this regard those definitions which exclusively refer to anatomic and macroscopic features that characterize the complete clinical picture of the disease have bearing, quite apart from the cellular structure of the newly formed tissues.

It is our intention to examine hereafter a particular anatomical type of primary cancer of the lung, which some researchers have not taken into consideration, but which in our opinion possesses in reality sufficient characteristics of its own to assume special position within the general picture of this disease. We mean by this the so-called pleural form of primary cancer of the lung.

This special name is explicitly mentioned in the classifications of P. Verga,[1] of Roussy and Huguenin,[2] of Olmer and Coll.,[3] of Liberti and Stella,[4] of Eizaguirre:[5] and it is applied to those particular forms of primary cancer of the lung, which rather than affecting the deeper parenchyma, prevalently acquire a surface development, spreading extensively over the pleura.

It is well known that during the development of primary cancer of the lung, affection of the serosa is a frequent event which is capable of assuming different features, such as formation of pleural effusion; diffuse or limited symphisis or thickening without any true tumorous propagation; localized appearances of bysmas and neoplastic masses; metastatizations in the form of waxen drops or plaques.

These are different aspects which are in each case to be explained by different stages of development which mark the general course of the disease.

The term *pleural form of primary cancer of the lung* is, however, intended to give prominence to those forms where the manifestation of heteroplastic tissues on the pleura is preponderant and almost exclusive, and where the affection of pulmonary parenchyma is absolutely marginal.

The precise definition of these forms must necessarily rest, therefore, not on the external aspects of the process alone but also on data of an histological nature.

In the observations which have been made by various researchers, even those where a fair number of cases are involved, it can be noted that the clinical picture does not occur with particular frequency and that as compared with the most common forms of hilar infiltrations, either the mas-

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sive or large nodular type, the cases where pleural affection is involved, always represent an extremely small group. In fact in the case histories of Verga and Botteri (op. cit.) they appear in three of 30 cases, in five out of a 100 in those of Liberti and Stella (op. cit.), in four out of 170 in the studies of Sival.[6]

In our studies, out of 82 cases of primary cancer of the lung, on which we have complete clinical and histological documentation, five presented neoplastic affections of a pleural nature. In reality in only four of them have the clinical and radiological data been supported by post-mortem examination and histological tests. In Case I in the table the patient died at home, two days after having left our institute by his own wish, our diagnostic conclusions are the result of a pleuroscopic examination that permitted direct visual examination of the pleura, which was uniformly invaded by large neoplastic lumps. Further deductions were made as a result of biopsy which made it possible to recognize bysmas and festoons of atypical epithelial elements, of a cylindric and cubic type, with a tendency to range themselves in several rows (Figures 1 and 2).

The individual course of each of the cases which form part of our collection prompts us to give particular consideration to three points which respectively concern the clinical and anatomical course of the disease and its histological characteristics.

Table I summarizes some of the *clinical data* of greatest importance:

TABLE I

Cases	Age in Years	Duration Clinical Course Months	Temp. Fever	Thoracic Pain	Pleural Effusion and its Nature
I : M	62	11	subfebrile initially	++	Abundant—hemorrhagic
II : W	56	6		++	Abundant—simple exudative
III : M	68	9		++	Abundant—hemorrhagic
IV : W	55	10	subfebrile with occasional recurrences	++	
V : M	43	8	subfebrile with occasional recurrences	++	Sacculated—simple exudative

The subjective symptomatology is largely dominated by the affection of the pleura, both when this is in the form of a pachypleuritis syndrome, without the formation of effusion (Case IV in our case histories) and when there is an exudative reaction, of a sero-fibrinous and sero-hemorrhagic type, the quantity of which is always considerable and re-forms readily. The latter type is the more frequent.

In the subjective and functional symptomatology which is usually connected with neoplastic pneumopathy, from the beginning thoracic pain and dyspnea are the phenomena of most importance: Usually there is no cough, when present it is slight and transitory, there is no abundant expectoration or hemoptysis.

FIGURE 1 (CASE I): Chest x-ray film (July 7th, 1953), after emptying the pleural effusion: considerable thickening of the pleural surface at the left side over collapsed lung.

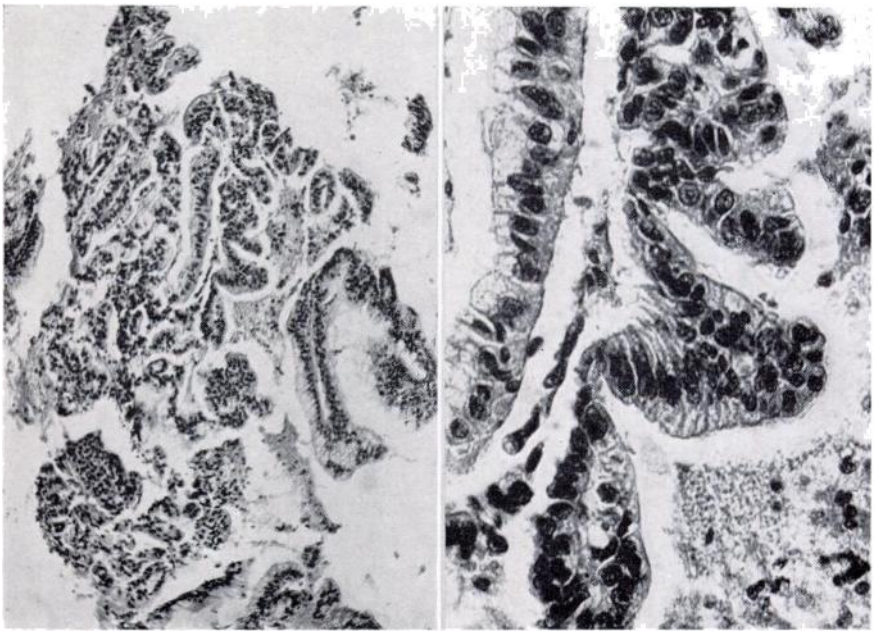

FIGURE 2 (CASE I): Biopsy fragment: neoplastic tissue constituted by epithelial elements of the cylindric type.

Modification of the temperature curve, in the cases studied by us, seems to have no particular trend. In the cases in question there were alterations of a febrile nature only in the initial phases (Case I), in some cases fever occurred from time to time, during the whole clinical course of the disease (Cases IV and V), while in other patients (Cases II and III) there were no febrile reactions during the whole course of the disease.

Thoracic pain, incessant, unremitting and refractory to analgesic action of any kind, are from the beginning localized in the costal area, and radiate in a strip along the thoracic wall and towards the shoulders.

Dyspnea, which is initially connected with physical efforts and particular bodily functions, is considerable from the beginning of the disease. Dell'Acqua[7] notes that it appears to have no true connection with extent of the exudative reaction and is caused, more than by any other factor, by the limitation of movements of the thoracic wall, rendered rigid by the spread of neoplastic tissue on the surface of the pleura.

The entire course of the disease, from appearance of the first clinical data, has in the cases studied by us been from six to 11 months, with an average duration of little more than eight months. This corresponds approximately to figures given by many researchers with regard to primary cancer of the lung: Verga and Botteri (op. cit.) : six months; Grissel and Knox[8]: seven and one-half months; King[9]: nine and one-third months; Liberti and Stella (op. cit.) : seven and one-third months.

Table II summarizes the principal *data of anatomical nature*:

TABLE II

	Side	Affection of the pleura	Pulmonary affection	Metastasis	Histological Type
I	Left	Costal pleura	——	——	Cylindrical cells
II	Right (Fig. 3)	Costal, interlobar and diaphragmatic pleura	Some subpleural bysmas	Lymph-glands liver-kidneys suprarenals	Small undetermined cells
III	Left (Fig. 4)	Costal, mediastinic and diaphragmatic pleura	Bysmas on the hilum with peribronchial location	Lymph-glands liver	Adeno-carcinoma mucigenous (Fig. 5)
IV	Left	Costal and diaphragmatic pleura	Parahilar block extending to lower lobe	Right lung-liver	Cylindrical cells trabecular papillar (Fig. 6)
V	Right	Costal, interlobar and mediastinic pleura	Some subpleural bysmas	Lymph-glands	Small undetermined cells (Fig. 7)

Leaving aside Case I, which was not anatomically checked, but which was clearly defined from an histological aspect as result of biopsy (Fig. 2), in all our other cases, there has always been evidence of a clear lack of proportion between the affection of the pulmonary parenchyma by the neoplastic mass and its development on the surface of the pleura.

In the lung, small or on occasion larger blocks of neoplastic tissue have been found in the vicinity of the hilum, in the form of plaques and bysmas located between the broncho-vascular formations and sometimes spreading

towards the upper or lower lobes. In general there has been no evidence of extensive proliferation inside the diameter of the large bronchial sections. Often, at this level, however, the mucosa was found to be clearly infiltrated. In one of our subjects (Case III) the neoplastic tissue showed immediately after the parahilar block, a clear tendency to spread to the peribronchial area, wrapping itself muff-like around the branches of the segmentary bronchial tubes.

In some other cases (II and V) large inter-parenchymal blocks were found only on the costal side, and appeared to be due to the direct spread of the effusion on the pleura towards the lung.

This parenchymal affection is always relatively moderate and in comparison, the spread of the tumor on the surface of the pleura has always been found to be extensive. Only in one case (IV) this occurred in the form of a large effusion which sealed together the visceral and parietal pleura and then wrapped itself around the whole lung. This was particularly true on the costal and mediastinic areas. In other cases the two leaves of the pleura remained separated, even though partially. This caused the creation of a cavity, which in some cases was large in size (Cases II and III) and in some smaller (Case V). This cavity was lined by thick neoplastic layers—up to a thickness of one centimeter—which formed on the visceral and parietal pleurae.

The possibility that the neoplastic invasion could proceed towards the inter-lobar pleura (Cases II and V), towards the mediastinal pleura (Cases III and V), and towards the diaphragmatic areas (Cases II, III and IV), was frequently evidenced in our cases, and had the usual characteristics.

Metastatic affection of the lymph nodes of the hilum, of the lung, and of

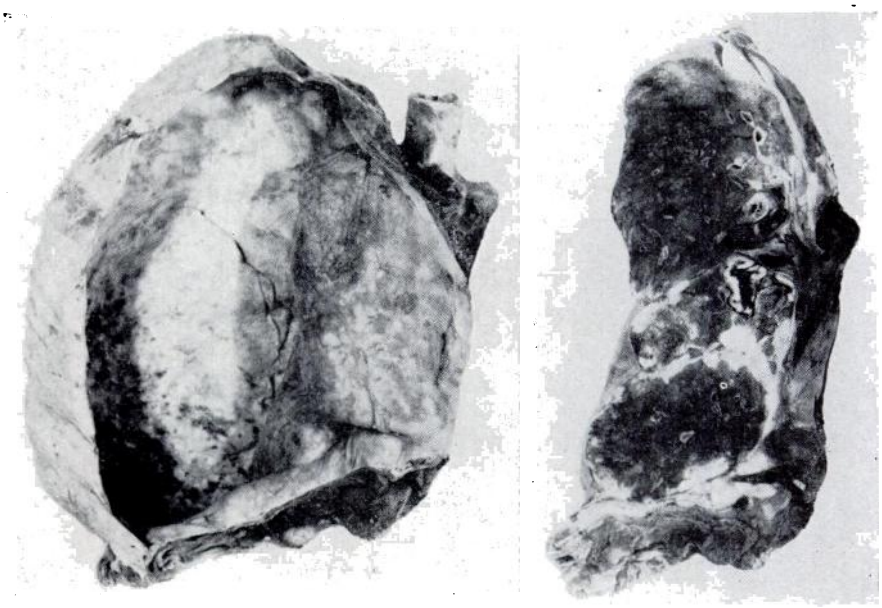

FIGURE 3 (CASE II): Right pleural space and collapsed lung stump; spreading of the neoplastic tissue over the surface of the costal pleura and over the interlobar and diaphragmatic surfaces.

the mediastinal lymph nodes, although often formed by bysmas and festoons of varying size, never assumed the character of a massive invasion. In some cases indeed (IV) there was no macroscopic evidence of an involvement worthy of note.

In three cases—out of the four on which anatomical studies were made—there was found to be a metastatic focus of other organs: liver, three times (Cases II, III, IV), kidneys and suprarenals, once (Case II), contra-

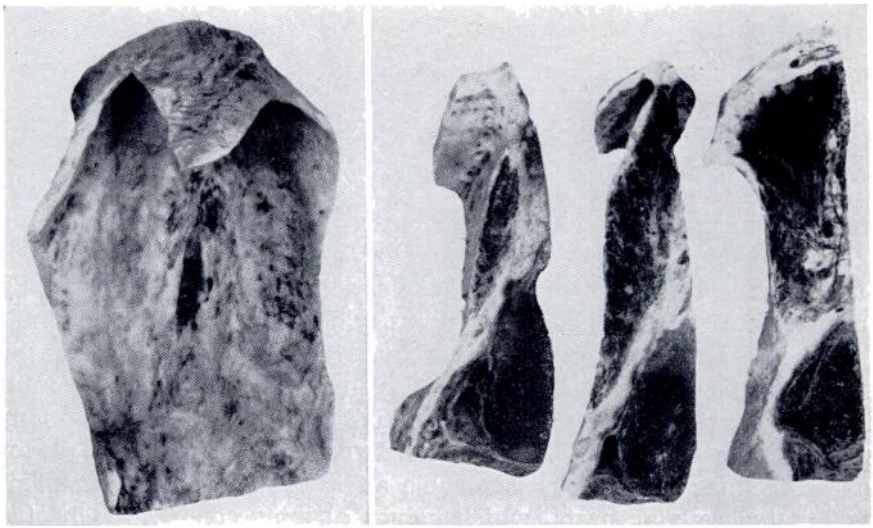

FIGURE 4 (CASE III): Left pleural space and collapsed lung stump: spreading of the neoplastic tissue over the surface of the costal and mediastinal pleura.

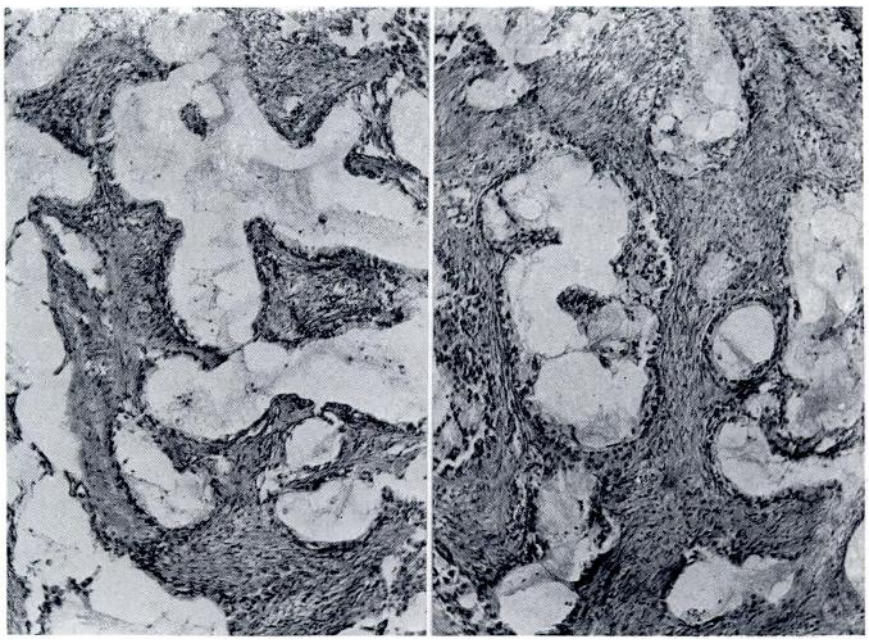

FIGURE 5 (CASE III): Histological fragment of the pleural surface: adeno-carcinomatous mucigen pattern on a thick collagen tissue.

lateral lung (Case IV), once.

With reference to the cases studied by us, Table II gives the histological appearance of the neoplasm. In the first place it is clearly noticeable that the pleural form of primary cancer of the lung has no predilection for any particular histological type. For this reason the cell structure of the substratum may be formed by small undetermined cells, or by cylindrical-polymorphous types, and indeed, by adeno-carcinomatose structures of a mucigenous nature. This is a general characteristic of all the diverse anatomical forms of primary cancer of the lung (hilar infiltrative, massive with one large nodule, or with multiple nodules) and as is known its histological nature may vary from case to case.

The epidermoid or squamous cell histological type was not represented in our cases. We certainly do not know to what degree this exclusion is valid, but even in other case histories (Botteri, Liberti and Stella) which include the pleural form, no reference is made to this latter oncotype.

From an histological viewpoint another aspect should be emphasized. On the surface of the pleura the neoplastic tissue is always associated with a stromatic collagenous component which is particularly abundant, and which attains even greater prevalence than the quota of epithelial cells. This basic hyperplastic reaction, is in part induced by the infiltration of neoplastic elements, and is partially accentuated by phenomena of stasis in the subpleural lymphatic network (Scalfi[10]). The above reaction sometimes causes a considerable alteration in the arrangement of the infiltrated cellular nests, which brings about a complete lack of con-

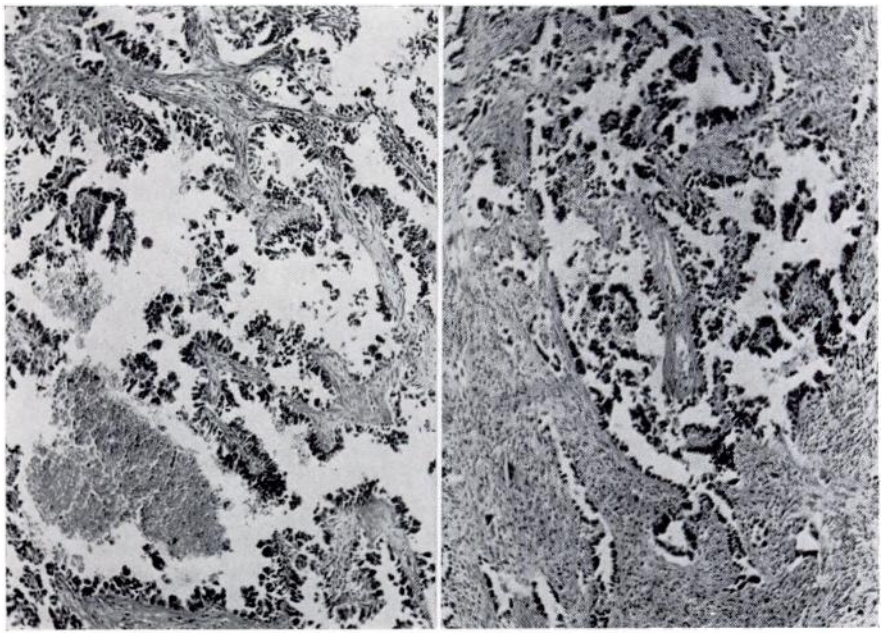

FIGURE 6A FIGURE 6B

Figure 6A (CASE IV): Parenchymal fragment: neoplastic tissue constituted by cylindrical-cuboid epithelium, in a papillary arrangement.—*Figure 6B* (CASE 4): Pleural fragment: same aspect, with a larger participation of connective stroma.

nection between the nature of heteroplastic tissues in the lung and those in the area of the pleura.

In this way, while in the lung there are varying types of arrangement, such as islands and solid cords, or tubercular, trabecular, papillar, adenomatous, etc., in the pleural area there is more commonly found a scirrhous type, with cellular formations of varying density, in which solid formations in general predominate. Of much greater rarity and of a barely perceptible type are trabecular and papillar formations, and those which resemble glandular formations (See figures 6 and 7).

Although the factors considered up to the present attribute to the pleural form of primary cancer of the lung certain characteristics which define with considerable clarity its clinical and anatomical physiognomy, they do not explain the causes and conditions which bring about the configuration of this complex structure. The fact that it is not brought about by single histological substrate, but that nearly all the cellular types of broncho-alveolar carcinoma contribute to its structure makes it still more difficult to determine the effective morphogenetic phases involved.

From the pattern of our cases and the examination of the observations of researchers who have preceded us, it seems possible to outline two conditions which are capable of giving rise to a surface development of primary tumor of the lung: Origin in subpleural and absolutely peripheral parenchymal sectors, and initial location in broncho-alveolar sectors immediately adjacent to the mediastinal pleura.

The attached diagram indicates this double possibility which in all

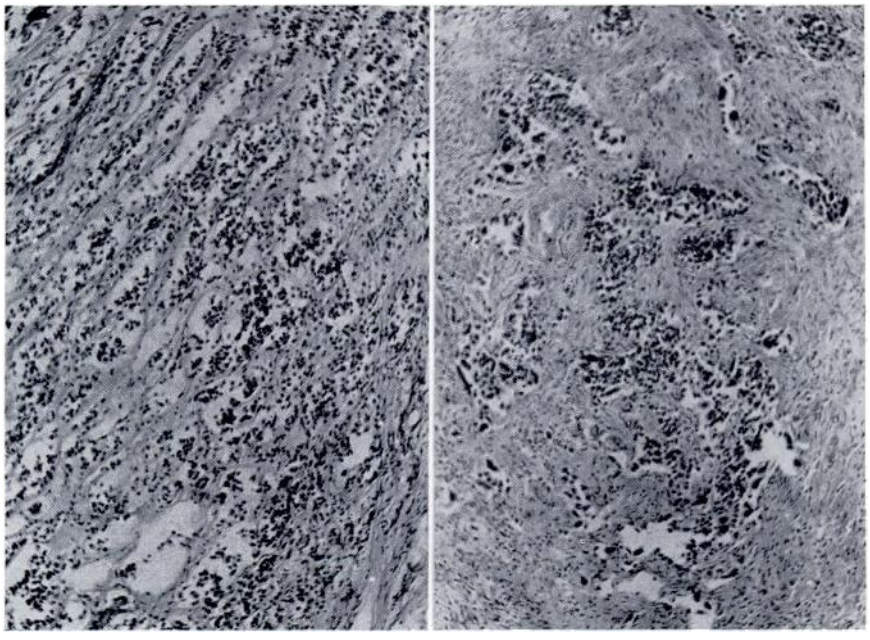

FIGURE 7A FIGURE 7B

Figure 7A (CASE V): Parenchymal fragment: neoplastic tissue of the kind of small-cell cancer.—*Figure 7B* (CASE V): Pleural fragment: nests of neoplastic cells on the background of a thick collagen tissue.

probability is to be considered linked to the adjacency of heteroplastic tissue of neoplasm to the pleural lymphatic network; this also leads one to believe that even in the first hypothesis the conditions which favor surface development may be given by propagation in a direct sense of the lymphatic stream; in the second hypothesis one finds a retrograde tendency, which also appears to lead to an extensive affection of the pleural covering.

Far from being explanatory, this statement is only a determination of the circumstances which bring about the anatomical picture in question. As in each individual sector of general and specialized oncology, there are numerous obscure points which the information and knowledge in our possession at present are insufficient to clarify.

SUMMARY

The pleural form of the primary cancer of the lung constitutes an infrequent, but absolutely particular type among the neoplastic lung processes. Its chief characteristic is that the neoplastic tissue, instead of involving the depth of the parenchyma of the lung, is almost entirely spread upon the pleural surface, becoming very similar to primary cancer of the pleura.

The histological analysis allows to differentiate it by finding cellular elements of broncho-alveolar derivations.

The authors have collected five cases of the pleural form out of a total group of 82 cases of primary cancer of the lung: in one of these a biopsy through pleuroscopy established the right diagnosis.

RESUMEN

La forma pleura del cáncer primitivo del pulmón constituye un tipo poco frecuente, pero muy peculiar entre los procesos neoplásicos pulmonares.

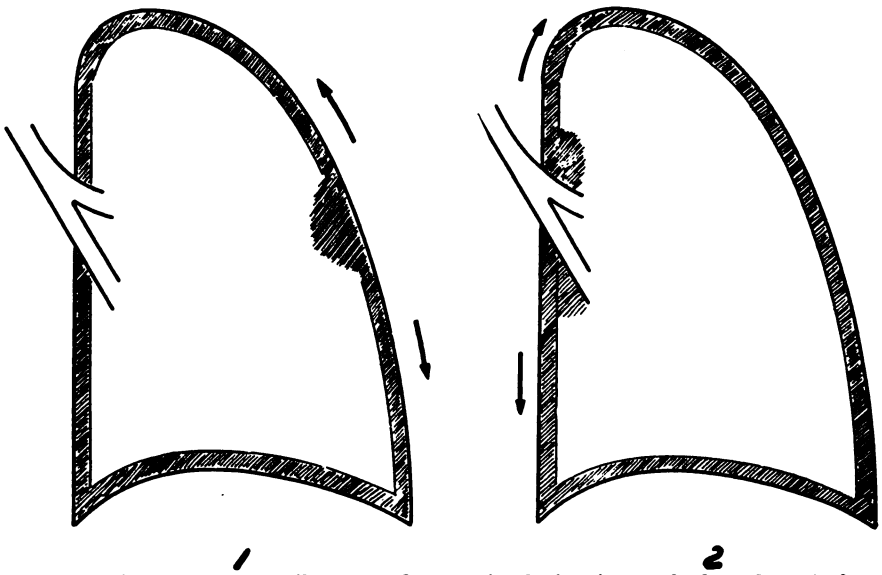

FIGURE 8: Scheme of possible morphogenetic derivations of the pleural form of primary lung cancer.

Su característica principal es que en lugar de invadir la profundidad del parénquima pulmonar se extiende casi completamente sobre la superficie pleural haciéndose muy semejante al cáncer primario de la pleura.

El análisis histológico permite diferenciarlo al encontrar los elemontos celulares de las derivaciones broncoalveolares.

Los autores han reunido cinco casos de la forma pleural de un total de 82 casos de cáncer pulmonar; en uno de estos una biopsia a través de la pleuroscopía estableció el diagnóstico correcto.

RESUME

La forme pleurale du cancer primitif du poumon constitue un type peu habituel mais tout à fait particulier des néoplasies pulmonaires. Sa caractéristique majeurs est que le tissu néoplasique au lieu de se développer dans la profondeur du parenchyme du poumon s'étend presque en totalité sur la surface pleurale, devenant très semblable à un cancer primitif de la plèvre.

L'analyse histologique permet de la différencier par la constatation d'éléments cellulaires d'origine broncho-alvéolaire.

Les auteurs ont recueilli cinq cas de forme pleurale sur un groupe total de 82 cas de cancers primitifs du poumon: dans l'un d'eux une pleuroscopie avec biopsie permit d'établir le diagnostic correct.

ZUSAMMENFASSUNG

Die pleurale Form des primären Lungenkarzinoms stellt einen seltenen, aber durchaus besonderen Typ unter den Lungenneoplasmen dar. Das Hauptkennzeichen dieser Art von Karzinom ist die fast ausschliessliche Ausbreitung neoplastischen Gewebes auf die pleurale Oberfläche an Stelle des Vordringens in die Tiefe des Lungenparenchyms. Somit wird dieser Krebs dem primären Pleurakarzinom sehr ähnlich.

Die Differenzierung ist durch die histologische Untersuchung möglich, indem zelluläre Elemente broncho-alveolären Ursprungs bei dieser Tumor-Art nachgewiesen werden können.

Die Verfasser haben 5 Fälle der pleuralen Form unter insgesamt 82 Fällen von primärem Lungenkarzinom gesammelt; in einem Fall wurde die richtige Diagnose durch thorakoskopische Probe-Excision gestellt.

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