Immunohistochemical Tumor-related Aspects in Diagnostic Mediastinal Lymph Node Extension in Broncho-pulmonary Carcinoma

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Broncho-pulmonary neoplasm is the leading cause of cancer death throughout the world (17% of male cancers and 12% of female cancer deaths). As a result, the medical management has been rigorously quantified in terms of clinical-histological characteristics and the invasive tumour stage, the degree of mediastinal lymph node extension and the presence of distant metastases determined with the TNM staging system that is recognised globally The x-ray examination reveals only pathological mediastinal lymph nodes that cause changes of mediastinal margins and the pleural reflection lines. The disadvantage of the traditional x-ray examination is the impossibility to identify the lymph nodes situated within the mediastinum. Also if the lymph nodes are hidden behind other tumour masses existing in the mediastinum, they cannot be discovered at the x-ray examination, which offers little information about the mediastinal structure: vessels, lung, pericardium, pleura, and thoracic wall. Due to the possibility to reveal all groups of pathological mediastinal lymph nodes, computed tomography is the first choice examination for the diagnosis of mediastinal adenopathies. Besides the traditional, cytological and histopathological methods that enable the identification of pulmonary neuroendocrine carcinoma, its malignancy degree and stage, the immunohistochemical methods are very valuable for the assessment of the evolution capacity of pulmonary neoplasia. The lung can be subjected to a large variety of complementary investigations.

Keywords: mediastinal lymphadenopathy, broncho-pulmonary neoplasm, pulmonary neuroendocrine tumours, radio-imaging examinations

Broncho-pulmonary neoplasm is the leading cause of cancer death throughout the world (17% of male cancers and 12% of female cancer deaths). Consequently, therapy management has been rigorously quantified in terms of clinical-histological characteristics and the invasive stage of the tumour, the degree of mediastinal lymph node extension and the presence of distant metastases determined with the TNM staging system that is recognised globally [1].

In the past decades, the great progress made in the field of diagnosis instruments has led to an increase in the number of early-stage tumours and atypical proliferative lesions that may cause differential diagnosis issues.

The new morphological investigation methods, especially immunohistochemistry and electron microscopy, have provided a large amount of information about tumour histogenesis, differentiation and proliferation, which has led to the reconsideration and reorganisation of the traditional classifications and the identification of new tumour subtypes[2].

Due to its diagnosing, staging, quantifying and therapy monitoring abilities, thoracic CT scan has become more than necessary for the assessment of mediastinal lymph node extension in broncho-pulmonary neoplasm.

The identification of the relationship with the interstitium is a diagnosis criterion of maximum specificity for the detection of neoplastic hilar adenopathies through spiral computed tomography – a standard investigation method with comparative interpolations in medical imaging.

This study intends to underline the role of medical imaging examinations in diagnosing mediastinal lymph node extension in broncho-pulmonary cancer. It will also reveal the clinical-morphological and anatomical inter-relationships that underline the importance of their detection in post-therapy staging and assessing of broncho-pulmonary neoplasm pathology in the mediastinal lymph nodes drained area.

The main objectives of this study are the following:

- to reveal and assess the criteria of radiography and computed tomography-based diagnosis of mediastinal lymphadenopathy;
- to study the mediastinal lymph node extension pattern of various morbid neoplastic entities of broncho-pulmonary location;
- to distinguish clinical-morphological and anatomical inter-relationships with interpolations specific to each group of mediastinal lymph nodes;
- to make topo-anatomical correlations of metastatic mediastinal adenopathy characteristic of various primitive broncho-pulmonary locations;
- to underline the impact of diagnosing the mediastinal lymph node extension on therapy management;
- to underline the importance of early detection of suspicious malignant mediastinal lymphadenopathy indicating that immediate histological confirmation is required;
- to underline the importance of spiral CT scan criterion for hilar mediastinal lymph node malignancy.

Experimental part

Materials and methods

A retrospective statistical analysis was performed on 134 cases of broncho-pulmonary cancer with mediastinal lymph node extension, studied with thoracic CT scan in the CT Laboratory of the Military Hospital Timisoara from

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January 2004 to December 2006. The patients underwent clinical-biological, bronchoscopic and histopathological examinations that helped establishing the diagnosis, the stage, the proper therapy management and, in some cases, the post-therapy assessment.

Each case was analysed based on clinical-biological, epidemiological, bronchoscopic, histopathological and immunohistochemical data taken from the medical examination request form and corroborated with the X-ray and CT scan results. The X-rays in the patient evaluation forms and the CT images taken in various density ranges to distinguish the morphological alterations of the mediastinal lymph nodes were re-examined [3].

Lung cancer is frequently insidious and does not produce any symptoms until the disease is advanced (the onset is often indicated by signs of neoplastic spread, metastases or complications – pneumonia, atelectasis, pleuro-pericardial effusion, pneumothorax, pneumo-mediastinum); the main manifestations are shortness of breath, metastases and paraneoplasms [5].

Pulmonary neoplasm can cause various lung syndromes (non-retractile consolidation syndrome, cavitary syndrome, retractile consolidation syndrome, pleural syndrome – in case of peripheral tumours adherent to the pleura) [4].

The general manifestations occur rather late and are associated with fever, weight loss and altered general state.

X-ray: lung neoplasms may show various radiological aspects: a solitary node with irregular margins, high growth rate and a tendency to abscess, or a thick-walled cavity with external spiculated contour and irregular internal contour (a sign of necrosis). Sometimes the only radiological signs in lung cancer are hilar/mediastinal adenopathy lobe/segmental atelectasis. Lymphangitis carcinomatosa may be identified in advanced stages.

CT: detects small tumours and helps the surgery recommendation depending on the degree of loco-regional and distant invasion (metastases); it allows the identification of adenopathies and mediastinal adenopathy groups.

The word *neuroendocrine* refers to tumours that form a part of the spectrum of lesions that have neuroendocrine differentiation and vary from well-defined neuroendocrine neoplasms (traditionally known as carcinoid tumours) to poorly differentiated malignant lesions with neuroendocrine properties exemplified by small-cell carcinoma. The classification of these lesions is controversial, although the current system seems both reproducible and clinically significant. Morphologically, neuroendocrine differentiation is defined by the typical organoid growth pattern; ultrastructurally, by the demonstration of the presence of neurosecretory dense core granules; and immuno-histochemically, by immunoreactivity to neuroendocrine markers like chromogranin A and synaptophysin or peptide hormones like serotonin, the adrenocorticotropic hormone and bombesin. Recently, a new category of lesions was introduced: large-cell neuroendocrine carcinoma. It is not certain whether these tumours are a distinct clinical-pathological entity or just a poorly differentiated carcinoma with false or aberrant neuroendocrine differentiation. This category needs further studies to determine whether there are significant differences in the prognosis and the reaction to therapy when compared to large-cell bronchogenic carcinoma[9].

An important clinical association of neuroendocrine carcinomas is the development of paraneoplastic syndromes, a consequence of the aberrant expression of the peptide hormones, including Cushing's syndrome and the syndrome of inappropriate ADH(antidiuretic hormone) secretion. Well-differentiated neuroendocrine carcinoma is associated with the carcinoid syndrome in approximately 10% of cases. The clinical symptoms of the neuroendocrine carcinoma of the lung vary with tumour size, location and biological activity. [7]. Endobronchial tumours symptoms include cough, wheezing and hemoptysis[6].

The classification of pulmonary neuroendocrine tumours is complex but rather confusing; it is based on Arrigoni's classification that in 1972 identified 3 categories of pulmonary neuroendocrine tumours (typical carcinoid, atypical carcinoid and small-cell carcinoid tumours) [1]. The current classification adds new categories, based on data provided by optical and electron microscopy and immunohistochemistry [5].

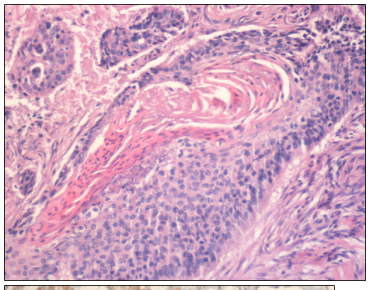

Fig.1. Squamous cell pulmonary carcinoma (hematoxilina – eozina) HEx200

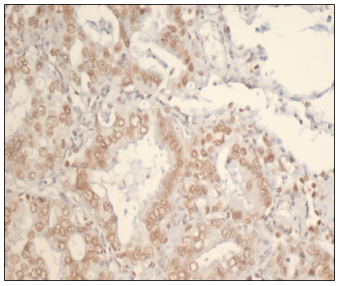

Fig.2. Pulmonary adenocarcinoma (Thyroid Transcriptor factor 1) TTF-1x200

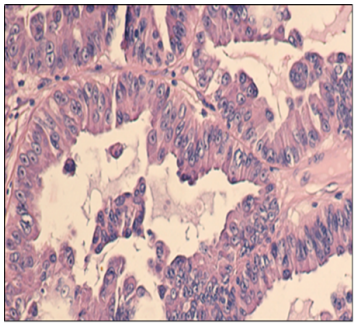

Fig.3 Pulmonary adenocarcinoma. HE x400

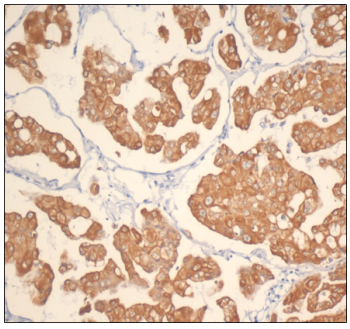

Fig.4 Pulmonary adenocarcinoma (cytokeratin-7) CK7 x200

Pulmonary neuroendocrine tumours

I. Common neoplasms with neuroendocrine aspects in optical microscopy

a) Typical carcinoid

b) Atypical carcinoid

c) Small-cell carcinoma

1. Pure

2. Mixed (small- and large-cell)

3. Combined

d) Large-cell neuroendocrine carcinoma

II. Pulmonary carcinoma, other than small-cell carcinoma, with ultrastructural or immunohistochemical neuroendocrie aspects

a) Adenocarcinoma (fig.2-4)
b) Squamous-cell carcinoma (fig.1, 6)
c) Large-cell carcinoma
III. Rare neuroendocrine neoplasms
a) Amphicrine neoplasms
b) Blastoma with focal neuroendocrine differentiation
c) primitive neuroepithelial tumours
d) Primitive pulmonary paraganglioma
e) "Anemone cell" neuroendocrine carcinoma
f) Neuroendocrine carcinoma with rhabdoid features etc.

Pulmonary neuroendocrine tumours are a group of distinct lesions with a large differentiation spectrum and clinical-biological behaviour varying from benign to highly malignant. The common characteristic of pulmonary neuroendocrine cells – normally observed in the respiratory epithelium (Kulchitsky cells) and found in very aggressive tumours – is the presence of neuroendocrine granules and neuroendocrine immunohistochemical markers. Some authors consider Kulchitsky cells as the origin of neuroendocrine tumours and their atypical hyperplasia (carcinoid tumourlets) as precursor lesions of small-cell carcinomas. However, such suppositions have not been confirmed yet [8].

Carcinoid tumourlets (atypical hyperplasia of the bronchiolar epithelium/multiple microscopic bronchiolar carcinomas) are small proliferations of neuroendocrine cells without clinical significance. They are seen very rarely, in lung tissue fragments resected for bronchiectasis, interstitial fibrosis, chronic abscesses, tuberculosis (less than 1%). They are more frequent in women and completely asymptomatic [1].

Macroscopically, carcinoid tumourlets are yellowish-grey nodes 3-4 mm in diameter (lesions larger than 0.5 cm are considered carcinoid tumours). Usually they are located in the peripheral areas of the lung, subpleurally or adjacent to the bronchioles, in the normal lung parenchyma or in a fibrous mass.

Microscopically, carcinoid tumourlets consist of the monotonous proliferation of cells with moderate quantities of eosinophilic or clear cytoplasmic content, and round/oval nuclei with fine granular chromatin [10].

Typical and atypical carcinoid tumours

These are lung tumours with a low malignant potential. According to their morphological aspect and their clinical-biological behaviour, they are divided into two categories: typical and atypical. They are rare in adults – about 1-2% of their total – but are the most frequent lung tumours in children and adolescents.

Only about 40% of patients with carcinoid tumours show symptoms when diagnosed. Symptomatology depends largely on tumour location: central, medial-pulmonary or peripheral. Central carcinoid tumours cause obstructive pneumonitis and hemoptysis, while peripheral carcinoid tumours are discovered accidentally, during thoracic x-ray performed for other purposes. Paraneoplastic syndromes may occur irrespective of location: carcinoid syndrome, Cushing's syndrome and acromegaly.

Peripheral carcinoid tumours are located in the subpleural lung parenchyma. Frequently they have no anatomic relationships with the bronchial tree. They are circumscribed but not encapsulated tumours and can infiltrate the adjacent parenchyma. They can be multiple and associated with multiple carcinoid tumourlets [12].

Central carcinoid tumours are larger than peripheral ones. Atypical carcinoid tumours are larger than typical ones [1]. Microscopically, both typical and atypical carcinoid tumours have an organoid growth pattern and a monotonous cytological aspect. Tumour cells have eosinophilic, fine granular cytoplasm and nuclei with fine granular chromatin. The nucleoli are visible only in atypical carcinoid tumours in which the chromatin pattern can be coarser.

There is a large variety of histopathological aspects that can occur both in typical and atypical carcinoid tumours: Rosetta-like, fusiform, trabecular, palisading, glandular, pseudofollicular, sclerosing papillary or diffuse infiltrating cells.

Tumour cells can be oncocyte-like, acinar-like, signet ring-like, mucus secreting or have a melanocytic aspect; ultrastructurally, they can have cilia or type II pneumocyte differentiation. Focal amyloid depositions, calcification and even ossification have been found in the stroma[11].

Criteria of differentiating typical from atypical carcinoid tumours:

- very reduced or absent mitotic activity in typical carcinoid tumours;
- 5-10 mitoses per 10 high-power fields in atypical carcinoid tumours;
- nuclear pleomorphism and hyperchromasia;
- absent in typical carcinoid tumours, characteristic of atypical carcinoid tumours;
- isolated, this criterion is not enough for the atypical carcinoid tumour diagnosis;
- hypercellularity areas with architectural disorganisation are seen in atypical carcinoid tumours;
- tumour necrosis occurs only in atypical carcinoids and is usually focal.

Ultrastructurally, typical carcinoid tumours have numerous dense core granules of variable shape and size. Oncocyte-like carcinoid tumours have both many mitochondria and dense core granules in their cytoplasm; they differ from pulmonary oncocytomas that do not have neuroendocrine granules. Neuroendocrine granules can be demonstrated also histochemically, with the Grimelius and Churukian–Schenk argyrophil methods.

Immunohistochemically, typical carcinoid tumours are positive for a wide range of neuroendocrine and hormone markers; atypical carcinoid tumours express a smaller amount of such markers. The most useful marker in the diagnosis of carcinoid tumours is chromogranin, followed by synaptophysin and Leu-7[5]..

Small-cell carcinoma

It is a highly malignant epithelial tumour consisting of cells of particular cytological characteristics: reduced cytoplasm, hyperchromatic nuclei with fine granular chromatin and lacking nucleoli, but with frequent mitoses. It is considered a distinct clinical-pathological entity due to its aggressive evolution and sensitivity to chemotherapy that distinguishes it from the other types of pulmonary carcinoma.

Small-cell carcinoma is a common tumour accounting for 20-25% of the total pulmonary tumours. This cancer type first occurs between 32 and 79 years of age, averagely around 60. It is twice more prevalent in men than in women and its etiopathogenic factor is smoking.

Due to its quick growth and chief central location, over 70% of patients are discovered in an advanced stage of the disease. Symptomatology includes cough, dyspnea, wheezing, hemoptysis, thoracic pain or post-obstructive pneumonitis. Small-cell carcinoma spreads in the mediastinum frequently and causes superior vena cava syndrome, recurrent nerve paralysis, dysphagia and a series of characteristic manifestations like antidiuretic hormone secretion problems, ectopic Cushing's syndrome and myasthenic-like syndrome[5].

According to the latest WHO classification, three types of small-cell carcinoma can be distinguished microscopically:

- *oat cell* (lymphocyte-like) type
- intermediary type
- mixed types.

Typical of small-cell carcinoma is the presence of large zones of tumour necrosis; isolated cells or cell groups are less frequent. In the necrotic zones hematoxyphilic incrustation of blood vessel walls (Azzopardi effect) occurs, due to incrustation by DNA from necrotic cells [2]. There is not a specific tumour growth pattern; tumour cells take the form of stripes, trabeculae, nests, tubules, palisades or even Rosetta-like arrangements. The stroma is rarely desmoplastic.

In small-cell carcinoma, tumour cells are small, rounded, oval or even fusiform, having hyperchromatic nuclei with fine granular chromatin and lacking nucleoli. The tumour has a general hyperchromatic aspect due to reduced cytoplasm and dense cell arrangement. Mitoses are very frequent, sometimes more than 10 per high-power field.

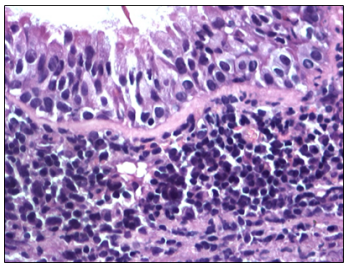

Fig. 5 Small cell lung carcinoma. HE x200

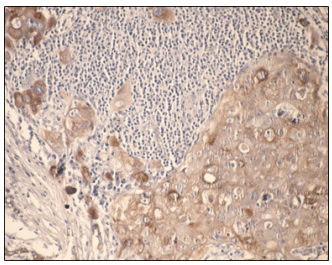

Fig.6 Lymph node metastasis in Squamous cell lung carcinoma. (pan-Cytokeratin) Pan-CK x200

Mixed small- and large-cell carcinoma, accounting for about 4-5% of the total of small-cell pulmonary carcinomas, is defined histologically as a combination of small and large cells, the latter representing at least 1% of the cell populations [1]. These two populations are either intricate or large lobular cells in a small-cell carcinoma.

Immunohistochemically, small-cell carcinomas(fig.5) do not differ from the other neuroendocrine tumours. Chromogranin, synaptophysin(fig.7) and Leu-7 are the most useful markers, especially when distinguishing mixed and combined types. Tumour cells may also be positive for neuron specific enolase, bombesin [4].

Cytokeratin and epithelial membrane antigen staining may be useful for differentiating small-cell carcinoma from a lymph node in small biopsies with crush artefact.

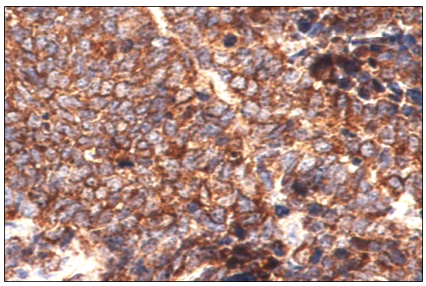

Fig.7 Smal-cell neuroendocrine carcinoma. Syn x200

Large-cell neuroendocrine carcinoma

This is a poorly differentiated, highly malignant pulmonary neoplasm with a neuroendocrine aspect in optical microscopy. However, this aspect must be confirmed immunohistochemically.

Large-cell neuroendocrine carcinomas have the following characteristics:

- organoid, trabecular or pseudo-Rosetta-like growth pattern;
- large, polygonal tumour cells with low nucleo-cytoplasmic ratio, coarse or vesicular chromatin and prominent nucleoli (fig.8);
- numerous mitoses (over 10 per 10 high-power fields);

Immunohistochemically, large-cell neuroendocrine carcinomas are positive for specific neuron enolase (100%), chromogranin (80%), Leu-7 and synaptophysin (40%), carcinoembryonic antigen and keratin (100%).

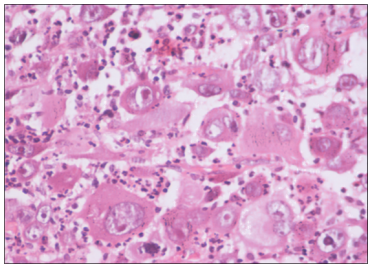

Fig.8. Undifferentiated large cell lung carcinomas. HE x 400

Ultrastructurally, large-cell neuroendocrine carcinomas differ from atypical carcinoid tumours in their smaller number of neurosecretory granules and the presence of intracytoplasmic lumens or desmosomal intercellular attachments – remnants of glandular or squamous differentiation[12].

Results and discussions

Evaluation of the efficiency of the radiology diagnosis criteria

Conventional x-ray was the first examination in all 134 cases of mediastinal adenopathy investigated imagistically. The investigation individualised only pathological mediastinal lymph nodes that cause a change of the mediastinal contours and pleural reflection lines; the lymph nodes located within the mediastinum and those hidden by other tumour masses that existed in the mediastinum were not revealed during the x-ray diagnosis.

Evaluation of the efficiency of CT diagnosis criteria

Diagnosis, staging and post-therapy evaluation of mediastinal lymph node extension in broncho-pulmonary cancer led to the identification of adenopathies in 134 cases. In 88 (65%) of the broncho-pulmonary cancer cases examined for diagnosis and staging, adenopathies were isolated and quantified as follows: stage N1 was identified in 31 cases, stage N2 in 34 cases and stage N3 in 23 cases (fig.9).

Post-surgery thoracic CT scan evaluation revealed mediastinal adenopathies in 17 (13%) cases of resected broncho-pulmonary neoplasms, which was an important argument for radio and chemotherapy association. The mediastinal adenopathies revealed in 29 (22%) cases during the examinations for post-radio and post-chemotherapy evaluation required that the treatment be continued or re-started.

The location and the round or oval shape that varied with the position of the section plan (parallel to or perpendicular on the long axis of the lymph node) were constant and defining diagnosis elements. The other semiologic features showed a certain variation whose clinical–morpho-pathological correlation enabled the establishing of susceptibility indicators for an

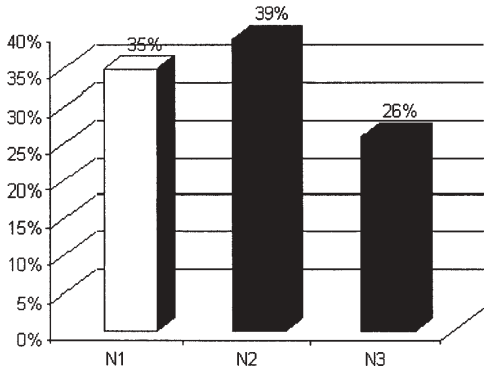

Fig 9. Results of N staging of the 88 cases of broncho-pulmonary carcinomas

Lymph node groups	CT-identified	X-ray identified
(1) Supraclavicular/scalene	22	2 (9%)
(2 right) Right upper paratracheal	132	122 (92%)
(2 left) Left upper paratracheal	44	39 (89%)
(3) Pre-and retro-tracheal	87	65 (75%)
(4 right) Right lower paratracheal	97	91 (94%)
(4 left) Left lower paratracheal	67	61 (91%)
(5) Aortopulmonary window	51	27 (53%)
(6) Anterior mediastinal	91	47 (52%)
(7) Subcarinal	166	68 (41%)
(8) Para-esophageal	45	8 (18%)
(9) Pulmonary ligament	28	20 (71%)
(10 right) Right tracheobronchial	158	132 (84%)
(10 left) Left tracheobronchial	64	59 (92%)
(11 right) Right intrapulmonary	51	45 (88%)
(11 left) Left intrapulmonary	15	9 (60%)
(12 right) Right lobe	48	39 (81%)
(12 left) Left lobe	27	19 (70%)
(13 right) Right segmental	19	12 (63%)
(13 left) Left segmental	12	8 (67%)
(14) Diaphragmatic	17	11 (65%)

Table 1
EVALUATION OF THE EFFICIENCY OF IMAGISTIC METHODS IN DIAGNOSING MEDIASTINAL ADENOPATHIES IN TERMS OF THEIR TOPO-ANATOMICAL LOCATION

etiopathogenic diagnosis that was confirmed with cyto- and histopathological data.

Broncho-pulmonary metastatic adenopathies occurred more frequently under conglomerated form in 57% cases and diffuse in 54% cases; homogeneous density was detected in 58% cases; internal calcification and iodophilia after the IV administration of the contrast substance were also present.

Size was the major semiotic factor of the CT diagnosis of mediastinal adenopathy. The transverse diameter of the scanned lymph node was taken into consideration.

Sizes between 0.5-1 cm were seen in 12% of cases, separating especially those lymph node groups that are not CT-revealed normally: 8, 9 and 14(table 1). Adenopathies with a 1-2 cm transverse diameter were identified in 13% of cases, while a 2-3 cm transverse diameter occurred in 23% of cases; larger adenopathies were detected in 52% of cases. The increasing malignancy degree demonstrated that susceptibility to malignancy increases with size.

The comparative evaluation of the efficiency of imagistic methods in diagnosing mediastinal lymphadenopathies (table 1)reveals the superiority of the CT scan over the x-ray examination in supraclavicular, anterior mediastinal and aortopulmonary groups.

The invasion preferences through lymph node extension in broncho-pulmonary cancer in various groups of drainage mediastinal lymph nodes are specific to area and histological type. The result is a faithful, feedback-type reflection of the location areas of the primitive lesions.

Pulmonary endocrine tumours have a high growth and metabolization rate and currently they are a cause of early mortality throughout the world.

Conclusions

The x-ray examination reveals only pathological mediastinal lymph nodes that cause changes of mediastinal contours and the pleural reflection lines.

The disadvantage of the traditional x-ray examination is the impossibility to identify the lymph nodes situated within the mediastinum.

Also if the lymph nodes are hidden behind other tumour masses existing in the mediastinum, they cannot be discovered at the x-ray examination, which offers little information about the mediastinal structure: vessels, lung, pericardium, pleura, and thoracic wall.

Due to the possibility to reveal all groups of pathological mediastinal lymph nodes, computed tomography is the first choice examination for the diagnosis of mediastinal adenopathies[3].

Computed tomography has poor specificity. Although the criteria of positive diagnosis of adenopathies (density, transverse diameter, the presence or absence or calcifications, iodophilia etc.) establish a clinical-morphological relationship, they are but susceptibility indicators for the etiologic diagnosis in which the confrontation with the clinic is primordial and only the anatomical-pathological examination can provide certitude. Given the challenges such pulmonary tumours can raise, the mission of the pathologist is to establish the histological diagnosis and to provide those data that are necessary for the clinical-pathological staging.

Besides the traditional, cytological and histopathological methods that enable the identification of pulmonary neuroendocrine carcinoma, its malignancy degree and stage, the immunohistochemical methods are very valuable for the assessment of pulmonary neoplasia evolution. The lung can be subjected to a large variety of complementary investigations. [1].

References

1. COMAN C., COMAN B.C.; Cancerul traheo-bronho-pulmonar în PROCA E.; Patologie chirurgicalã Volum V, Partea a III-a; Editura Medicalã, Bucureºti 1991; p.160-191;
2. COULOMB M., FERRETTI G., RANCHOUP Y.; Mediastinum: plain film, CT and MR correlations în LISSNER J., BAERT A.L., POKIESER H., VAN WAES P.F.G.M.; Imaging of the chest: an update; Syllabus; categorical course ECR 1991; p. 1-10
3. DIACONESCU N., ROTTENBERG N., NICULESCU V.; Noþiuni de anatomie practicã; Editura Facla Timiºoara 1979 p. 149-177
4. DIXON A.K., FLOWER C.D.R.; The Somato Plus in mediastinum: preliminary observations în FUCHS W.A.; Advances in CT, European Scientific User Conference Somatom Plus; Zurich, march 1990 ;p. 179-191
5. FELD R., PAYNE D., SHEPHERD F.A.; Small cell lung cancer în SHIELDS T.W.; General thoracic surgery; Williams & Wilkins 1994; p. 1241-1271
6. FRIJA J.; Les autres techniques d'imagerie du thorax în FRIJA J.; Radiologie du thorax; Masson, Paris, Milan, Barcelona 1995; p. 75-90
7. GALBENU P.; Morfopatologia cancerului bronhopulmonar în HORVAT T., DEDIU M., ÞÂRLEA A.; Cancerul bronhopulmonar Universul SA Bucureºti 2000; p.. 47-71
8. GAMSU G.; Lymph nodes of the mediastinum în MARGULIS A.R., GOODING C.A.; Diagnostic Radiology; Department of Radiology University of California, San Francisco 1984; p. 451-458
GAMSU G.; The mediastinum în MOSS A.A., GOMSU G., GENANT H.K; Computed tomography of the body with magnetic resonance imaging; W.B.Saunders Company; USA 1992 p. 43-118
10. GEORGESCU S., Explorarea CT a toracelui în LUNGEANU M.; Manual de tehnicã radiologicã; Editura Medicalã; Bucureºti 1988; pag. 505-512
11. GINSBERG R.J.; Carcinoid tumors în SHIELDS T.W.; General thoracic surgery; Williams & Wilkins 1994; p. 1287-1297
12. GOLDBERG S.N., RAPTOPOULOS V., BOISELLE P.M., EDINBURGH K.J., ERNST A.; Mediastinal lymphadenopathy: diagnostic yield of transbronchial mediastinal lymph node biopsy with CT fluoroscopic guidance-initial experience în Radiology Volume 216,Number 3; September 2000; p. 764-768

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