PARANEOPLASIC SYNDROMES ASSOCIATED TO THE PULMONARY CANCER: ETHIOPATHOGENY

LIVIA MIRELA POPA

PhD candidate University “Lucian Blaga” of Sibiu

Abstract: The paraneoplastic syndromes are clinical and biological nonspecific manifestations that appear at the patients with malignant neoplasia. Those disorders are caused by the direct action, local and mechanical action of the tumor on the organ or tissue where is developed, but it is not in a direct rapport with the local action of the metastasis of the primary tumor. The paraneoplastic tumors associated to the pulmonary cancer are numerous and extremely varied. They are produced through the secretion of the ectopic hormones by the tumoral tissue. The producing of ectopic hormones or their precursors that are peptides is a characteristic for all the types of cancer, but in the pulmonary cancer the incidence of the clinical manifestations correlated with the secretion of ectopic hormones is relatively raised. It seems that the clinical syndromes may appear only if the neoplastic tissue is capable of metabolise the precursors the polypeptides in bioactive hormones.

Keywords: etiopathogeny, ectopic hormonogenesis, theories

Cuvinte cheie: etiopatogenie, hormonogenetă, ectopică, teorii

Rezumat: Sindromele paraneoplazice sunt manifestări clinice și biologice nespecifice care apar la bolnavii cu neoplasii maligne. Aceste tulburări nu sunt cauzate de acțiunea directă, locală, mecanică a tumorii asupra organului sau de esutului în care se dezvoltă, după cum, nu se află în raport direct cu acțiunea locală a metasetelor tumorii primitive. Sindromele paraneoplazice asociate cancerului bronhopulmonar sunt numeroase și extrem de variate. Ele sunt produse prin secreția de hormoni ectopici de către esutul tumoral. Producerea de hormoni ectopici sau precursori lor, care sunt pep tide, este caracteristică pentru toate tipurile de cancer dar, în cancerul bronhopulmonar, incidența manifestărilor clinice, corelația de hormoni ectopici este relativ ridicată. Se pare că, sindromele clinice pot să apară, numai dacă esutul neoplazic este capabil să metabolizeze polipeptidele precursori, în hormoni bioactivi.

SCIENTIFIC ARTICLE OF BIBLIOGRAPHIC SYNTHESIS

Etiopathogeny. In order the paraneoplastic syndromes to appear is absolutely necessary that in the patient’s body to develop a malignant tumor. In some circumstances, the apparition of those syndromes is conditioned by the intervention of several sinergic factors, but sometimes the same paraneoplastic manifestation may be produced through differente mechanisms. It is very probable the existence of a predisposing factor, individual, that explains the rarity of the paraneoplastic syndromes in comparison with the frequency of the malignant tumors. To explain the producing of the different paraneoplasia emitted a series of theories, among which some were confirmed in this purpose (7,8), and other only have an hystorical value.

The toxic theory, the first emitted theory, supposes the existence of a toxic substance that would grow up in the cancerous cell or could result from the resorption of the tumoral or peritumoral necrosis.

The allergic theory is somehow a variant of the toxic one. The antigen, in these cases, could be an elaborated product of the cancerous cell or could result from the catabolism or its destruction.

The endocrine theory is today proved as being valid in a series of paraneoplastic manifestations. It appeared the notion of ectopic hormonogenesis, through which it is understood the elaboration of a hormone, at distance from the endocrine gland that is secreted normally, by a tissue that usually doesn’t produce hormones. Most of the hormonale syndroms, at the patients with cancer, are linked to the production of peptides or proteic hormones. A peptic hormone is encoded, in general, by ARNm, that is transferred in a bigger molecule of prohormone, that suffers a series of post-translational modifications, inclusive clivage, glicosilation and others.(2) The tumoral cells of the nonendocrine organs is bridging, frequence, diverse compartments way that leads to the pro-hormone activation, determining the apparition of the biological active hormone, to secrete diverse substances. As a result of the defects at the level of the process of apparition of the proteins or of the post-translational modifications, in general, the tumoral cells may produce proteins that are similar in structure, but are biologically less active than the normal hormones. So, a neoplastic patient may have increased serical concentrations of immunoreactive hormones, in the absence of clinical syndromes given by the hormonal excess.(7,8) Most of the endocrine neoplastic syndromes appear only with tumors from the neuro-endocrine tissue or of the neural growing (the pulmonary cancer with small cells, carcinoind tumors). The genetic mechanism that intervenes in the production of a hormone by a cell that normally doesn’t produce it isn’t clear yet.

The carential theory may explain numerous paraneoplastic manifestations. In the last evolution phases of the cancers, probably, a global nutritional carential diet accentuates or facilitates the apparition of parenchimal alterations. So, it is explained the production of the carential encephalopathies and
of other nervous lesions. The carential diet in an essential factor of the metabolism of the nervous substance (vitamine, enzyme) may cause paraneoplastic neurological syndromes. The carential diet in tiamine, riboflavin, nicotinic acid and pantothenic acid may cause the lesions of sensitive neuropathy and of the mixte polinevrites. A carence in the vitamine E, could have a rule in the apparition of the paraneoplastic muscular syndromes.(10)

The anoxic theory is invoked to explain the apparition of the osteo-articular paraneoplastic manifestations and of a paraneoplastic policytemia. The point of departure of this theory is linked of the finding that, these syndroms are very frequent in the intratoracic tumors, by there are analogies with the digital hypoparhesia from the congenital cyanosis cardiopathies and with the polymetrias from diverse chronic pulmonary affections. In those cases intrapulmonary arterio-venous bridging would produce a desaturation in oxygen of the blood and would determine anoxia in the digital extremities, that would have as result the apparition of the modifications characteristic to the syndrome.

The nervous theory was emitted to explain the production of the paraneoplastic osteo-articular manifestations. It is based on clinical findings such as: the section of the vague nerve determines the disparition of the osteo-articular syndrome. The same result it may be obtained through the section of the intercostal nerves on the part with the tumor.(10) Sometimes, the simple section of the vague determines the retrocession of the paraneoplastic ginecomasty. In the Schwartz-Bartter syndrome it had been showed that, the volenic variations produced through the vlo-receptors and through the vagal influx, influences the secretion of antidriuretic hormone. The invasion of the vagues, through the tumor, would destroy the inhibitory fibers and would determine a permanent defenration of the secretion of the antidriuretic hormone.

The viral theory didn’t proved valable only to explain the apparition of the herpes zoster during cancers. After some authors some of the neurological syndromes have the same etiology. In the cerebellar paraneoplastic syndromes, it couldn’t be evidetnted a morphological inflammatory component, and in the affected nervous cells, sometimes, inclusion bodies. The place of the lesions, their type, their propagation, suggest the intervention of a virus.(2,10)

The genetic theory sustains that at the origine of the paraneoplastic syndroms stands a predisposition, an ereditary fragility of the system interested by paraneoplastic manifestations. The carential factors or other factors that would action on this background. So, there could be lesions of metabolic deficiency of a genetic cause, on which several factors may act. So, it would be explained the production of nervous lesions, tardive cutaneous porphyria. The depression of one gene would explain diverse pathological secretions of the nervous cells (hormones, fetal antigens, isoenzymes).(10)

The theory of the common origin results from the unknowing causes of cancer and from the fact that often the paraneoplastic syndromes are previous to the apparition of the symptoms owned by the tumor itself. The same, it pleads for the analogy of the neurologic syndromes with the neuro-anemic syndrome in the pernicious anemia. The symptoms and nervous lesions, in this type of anemia, are not the complications of the disease, but are part of its sympathomatology, having the same production mechanism.

The immunologic theory (relationship between tumor-host). Considering that sometimes, the tumor appears at a very long interval from the installation of the paraneoplastic syndrome, some consider it as a pre-cancerous state. In the discussion are taken some of the collagenosis, sclerodermy and dermatomiositis. Hemolytic anemias that accompany some cancers may be caused by anti-bodies, as an expression of the body against the tumor, but it could represent also a pathologic production of the tumoral cells.(10) The intervention of an autoimmune mechanism is taken into consideration for a series of paraneoplastic manifestations such as: cutaneous issues, collagenosis, neurological affections, paraneoplastic thrombotic endocarditis.

Table no. 1. Usual endocrine paraneoplastic syndromes (7)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Proteins</th>
<th>Tumors that usually associates these syndromes</th>
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</thead>
<tbody>
<tr>
<td>Hypercalcemia</td>
<td>Parathyroid hormone (PTH)</td>
<td>The pulmonary cancer without small cells; Breast cancer; renal cell carcinoma; Head and throat cancer; Myeloma</td>
</tr>
<tr>
<td>Cushing Syndrome</td>
<td>Adrenocorticotropic Hormone (ACTH)</td>
<td>Small cells pulmonary carcinoma; Head and throat cancer; pulmonary cancer without small cells</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>Growth Hormone (GH)</td>
<td>Carcinoid; small cells pulmonary cancer; Tumors of the pancreatic insular cells</td>
</tr>
<tr>
<td>Ginecomastia</td>
<td>Human choronic Gonadotropin (hCG)</td>
<td>Testicular cancer; Pulmonary cancer; Carcinoid tumors of the lung and of the gastrointestinal tract</td>
</tr>
<tr>
<td>Hypoglycumia</td>
<td>Growth factor 2 similar insulin (IGF-2)</td>
<td>Sarcomas</td>
</tr>
</tbody>
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BIBLIOGRAPHY


