PARANEOPLASIC SYNDROMES ASSOCIATED TO THE PULMONARY CANCER: ETHIOPATHOGENY

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Abstract:*The paraneoplasic 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 developped, but it is not in a direct rapport with the local action of the metastasis of the primary tumor.The paraneoplasic tumors associated to the pulmonary cancer are numerous and extremly 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 neoplasic tissue is capable of methabolise the precursors the polypeptides in bioactive hormones.*

Cuvinte cheie: *etiopatogenie, hormonogenezã ectopicã, teorii*

Rezumat: *Sindroamele paraneoplazice sunt manifestãri clinice □i biologice nespecifice care apar la bolnavii cu neoplazii maligne. Aceste tulburãri nu sunt cauzate de ac□iunea directã, localã, mecanicã a tumorii asupra organului sau □esutului □n care se dezvoltã, dupã cum, nu se aflã □n raport direct cu ac□iunea localã a metastazelor tumorii primitive. Sindroamele paraneoplazice asociate cancerului bronhopulmonar, sunt numeroase □i extrem de variate. Ele sunt produse prin secre□ia de hormoni ectopici de cãtre □esutul tumoral. Producerea de hormoni ectopici sau precursorii lor, care sunt peptide, este caracteristicã pentru toate tipurile de cancer dar, □n cancerul bronhopulmonar, inciden□a manifestãrilor clinice, corelatã cu secre□ia de hormoni ectopici, este relativ ridicatã. Se pare cã, sindroamele clinice pot sã aparã, numai dacã □esutul neoplazic este capabil sã metabolizeze polipeptidele precursorii, □n hormoni bioactivi.*

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Ethiopathogeny. In order the paraneoplasic syndromes to appear is absolutely necessary that in the patient′s body to develop a malignant tumor. □n some circumstances, the apparition of those syndroames is conditionated by the intervention of several sinergic factors, but sometimes the same paraneoplasic manifestation may be produced through differente mechanisms. It is very probable the existance of a predisposing factor, individual, that explaines the rarity of the paraneoplasic 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 resorbtion 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 paraneoplasic 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 peptidic hormone is encoded, in general, by ARNm, that is transfered 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, freqently, 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 neoplasic 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 neoplasic syndromes appear only with tumors from the neuro-endocrine tissue or of the neural growing (the pulmonary cancer with small cells, carcinoid 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 paraneoplasic 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

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of other nervous lesions. The carential diet in an esential factor of the methabolism of the nervous substance (vitamine, enzyme) may cause paraneoplasic 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 role in the apparition of the paraneoplastic muscular syndromes.(10)

The anoxic theory is invoked to explaine the apparition of the osteo-articular paraneoplasic 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 hypocratism from the congenital cyanosis cardiopathies and with the policytemias 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 a result the apparition of the modifications characteristic to the syndrome.

The nervous theory was emitted to explain the production of the paraneoplastic ostheo-articular manifestations. It is based on clinical findings such as: the section of the vague nerve determines the disparition of the ostheo-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 volemic variations produced through the volo-receptors and through the vagal influx, influences the secretion of antidiuretic hormone. The invasion of the vagues, through the tumor, would destroy the inhibitory fibers and would determine a permanent defrenation of the secretion of the antidiuretic hormone.

The virusal 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 evidentiated 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 sustaines that at the origine of the paraneoplasic syndromes stands a predisposition, an ereditary fragility of the system interested by paraneoplasic manifestations. The carential factors or other factors that would action on this background. So, there could be lesions or methabolic 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 cancerous 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 pleades 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 sympthomatology, having the same production mechanism.

The imunologic 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 disscussion are taken some of the collagenosis, sclerodermy and dermatomiositis. Hemolytic anemias that acompany 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 paraneoplasic syndromes (7)

Syndrome	Proteins	Tumors that usually associates these syndromes
Hypercalcemia in neoplasia	Peptide-like the parathyroid homone (PAHP) Parathyroid hormone (PTH)	The pulmonary cancer without small cells; Breast cancer; renal cell carcinoma, bladder carcinoma; Head and throat cancer; Myeloma
The syndrome of inadequate secretion of vasopressin (SSIADH)	Arginin vasopressin (AVP) Atrial natriuretic peptide	Small cells pulmonary carcinoma; Head and throat cancer; pulmonary cancer without small cells
Cushing Syndrome	Adrenocorticotropic Hormone (ACTH) Corticotropine Liberating hormone (CRH)	Small cells pulmonary cancer; Carcinoid tumors
Acromegaly	Liberating hormone of the growth hormone (CRH) Growth Hormone (GH)	Carcinoid; small cells pulmonary cancer; Tumors of the pancreatic insular cells
Ginecomasty	Human chorionic Gonadotropin (hCG)	Testicular cancer Pulmonary cancer Carcinoid tumors of the lung and of the gastrointestinal tract
Hypoglycemia of the tumoral non-insular cells	Growth factor 2 similar insuline (IGF-2)	Sarcomas

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