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CASE STUDY

Non-small-cell lung cancer with multiple paraneoplastic syndromes

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Non-small-cell lung cancer with multiple paraneoplastic syndromes. I. Monsieur, M. Meysman, M. Noppen, J. de Greve, O. Delhove, B. Velckeniers, D. Jacobvitz, W. Vincken. ©ERS Journals Ltd 1995.

ABSTRACT: We describe the case of a patient with multiple paraneoplastic syndromes, six in total, associated with a non-small-cell cancer of the lung. In this single patient we found hypertrophic pulmonary osteoarthropathy, hyperkeratosis of palms and soles, erythema annulare centrifugum, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), and ectopic andrenocorticotrophic hormone (ACTH) and calcitonin production.

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Various remote effects of cancer or paraneoplastic syndromes are common in lung cancer, and may be the first manifestation of the disease or its recurrence [1]. Neuromuscular, vascular, haematological and metabolic syndromes, as well as syndromes involving the connective and skeletal tissues and skin can be distinguished.

Some of these syndromes are more specifically associated with a particular cancer histology. Hypertrophic pulmonary osteoarthropathy (HPO) has most often been described in association with non-small-cell lung cancer (NSCLC). Adrenocorticotrophic hormone (ACTH) secretion is almost always associated with small-cell lung cancer (SCLC) [2]. Usually only one and more infrequently two of these syndromes occur synchronously or metachronously in a single patient. The patient described here synchronously presented six paraneoplastic syndromes.

Case report

A 58 year old man with a smoking history of 40 cigarettes a day for 30 yrs and chronic obstructive lung disease presented with diffuse pain in both legs, generalized muscle weakness, and a weight loss of 18 kg over a period of 6 weeks.

Physical examination revealed that the patient had dark coloured skin, and was nearly cachectic with a weight of 52 kg. He was afebrile and vital signs were normal. Reduced breath sounds and dullness on percussion were noted over the left lung base. Thyroid palpation was normal. Hands and feet showed a convexity of the nails and enlargement of the distal phalanges of the fingers and the toes. Palpation of the anterior aspect of both tibias and femurs was very painful, especially close to the knees and ankles. There was neither swelling nor erythema of these joints. In addition, hyperkeratosis of the palms and soles was observed. During his hospital stay, the patient developed a migrating erythema annulare centrifugum on the chest, abdomen and gluteal region, as well as purpura on both legs.

Serum hyponatraemia (132 $mEq \cdot L^{-1}$) and hypokalaemia (2.7 $mEq \cdot L^{-1}$) were present. Arterial pH was 7.45. Renal function was normal (urea 50 $mg \cdot L^{-1}$, and creatinine 6.4 $mg \cdot L^{-1}$). Urinary sodium and potassium concentrations were 74 and 44 $mEq \cdot L^{-1}$, respectively. Serum osmolality was 279 $mOsm \cdot kg^{-1}$ H_2O and urine osmolality was 308 $mOsm \cdot kg^{-1}$ H_2O. Urinary cortisol excretion varied between 174 and 459 $\mu g \cdot 24\ h^{-1}$ (normal value 20–90 $\mu g \cdot 24\ h^{-1}$). Plasma levels of cortisol and ACTH were 333 $\mu g \cdot L^{-1}$ (elevated) and 45.1 $\mu g \cdot L^{-1}$ (within normal limits), respectively.

After administration of 100 μg corticotrophin-releasing hormone (CRH), plasma cortisol and ACTH rose by 19.5 and 75.5%, respectively. The flat cortisol response to CRH (<20% increase) indicates ectopic ACTH secretion. Serum aldosterone level was normal, whilst the antidiuretic hormone (ADH) level was inappropriately high (4.3 $ng \cdot L^{-1}$, normal value 0–2 $ng \cdot L^{-1}$ for plasma osmolality of 285 $mOsm \cdot kg^{-1}$ H_2O). Calcitonin level was 655 $\mu g \cdot L^{-1}$ (normal value less than 100 $\mu g \cdot L^{-1}$). Serum concentrations of calcium and phosphorus were normal. Carcinoembryonic antigen (CEA) was <3 $\mu g \cdot L^{-1}$ (normal); and neuron-specific enolase (NSE) was 20.5 $\mu g \cdot L^{-1}$ (normal value <12.5 $\mu g \cdot L^{-1}$). Thyroid function was normal.

Chest roentgenography showed an alveolar infiltrate in the left lower lobe and a prominent left hilum. Sputum

cytology revealed malignant epithelial cells. Bronchoscopic examination revealed extrinsic compression of the left wall of the distal trachea and of the left main-stem bronchus, with submucosal infiltration of the left lower lobe bronchus. Biopsies of the bronchial mucosa revealed a poorly differentiated adenocarcinoma. Mediastinoscopy was performed because of uncertainty about some retrocaval adenopathies observed on the computed tomography (CT) scan. Histological examination of these lymph nodes demonstrated invasion by poorly differentiated adenocarcinoma. The tumour showed areas with poorly differentiated glandular structures, as well as more solid areas and focal area with necrosis (fig. 1). The areas with glandular structures and solid structures showed a diffuse pancytoplasmatic positivity for cytokeratin (fig. 2), as well as for periodic-acid-Shiff (PAS) (fig. 3), and intense immunohistochemical positivity for CEA (fig. 4) and for neuroendocrine marker (synaptophysin) (fig. 5). The positivity for chromogranin stained less intense. Staining for ACTH and ADH was not performed.

Radionuclide bone scanning revealed osteoblastic activity at the ends of the long bones of upper and lower limbs, as well as in toes and fingers. Radiographs of these sites demonstrated periostal new bone formation as well as widening of the distal phalanges of the fingers.

Ultrasound examination of the thyroid did not reveal focal lesions, although there was a goitre. A brain CT scan was normal. Benign prostatic hypertrophy was seen on ultrasound. An abdominal CT scan only revealed a

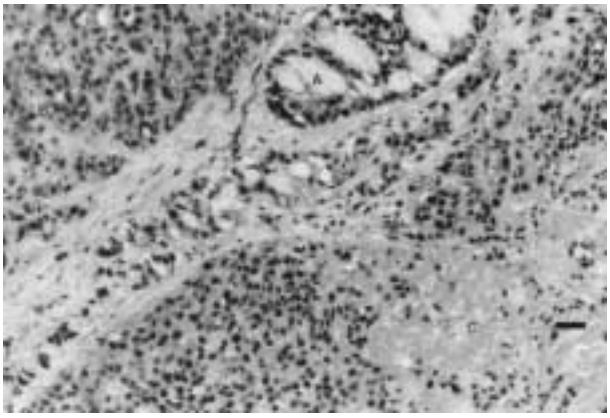

Fig. 1. – Poorly differentiated adenocarcinoma. A: area with poorly differentiated glandular structures; B: area with more solid pattern; C: large area of necrosis. (Haematoxylin and eosin staining; internal scale bar=50 μm).

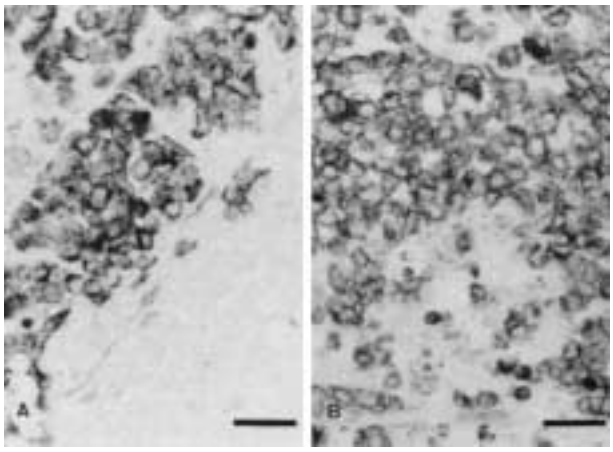

Fig. 2. – Poorly differentiated adenocarcinoma. Areas with more solid pattern. The tumour cells show a diffuse cytoplasmic positivity for cytokeratin immunohistochemical staining: A) CAM 5.2; and B) KL1. (Internal scale bar=50 μm).

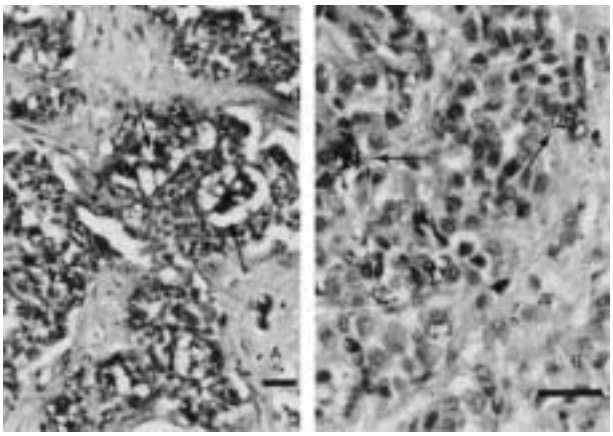

Fig. 3. – Poorly differentiated adenocarcinoma. A) Area with poorly differentiated glandular elements. The luminal spaces are PAS diastase positive (arrows). B) Area with more solid pattern but intracellular structures are PAS diastase positive (arrows). PAS: periodic acid Schiff. (Internal scale bars: 50 μm).

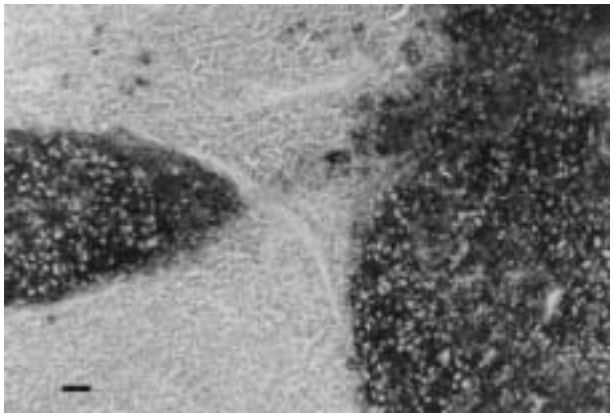

Fig. 4. – Metastasis of the poorly differentiated adenocarcinoma in a mediastinal lymph node with a diffuse strong positivity for immunohistochemical staining with carcinoembryonic antigen (CEA). (Internal scale bar=50μm.)

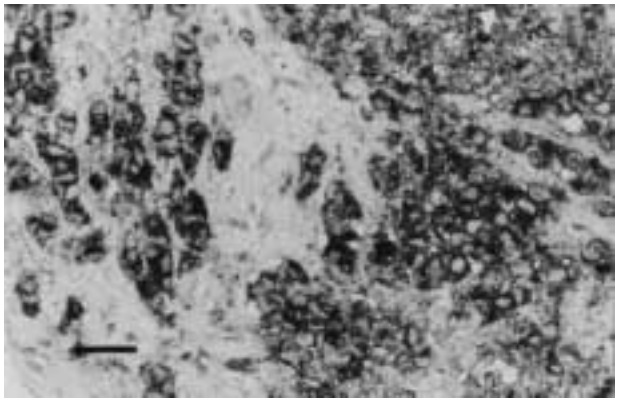

Fig. 5. – Poorly differentiated adenocarcinoma with neuroendocrine feature. Immunohistochemical staining for synaptophysin shows diffuse positivity of all tumour cells. (Internal scale bar=50 μm).

cortical cyst in the left kidney. Gastric endoscopic examination was normal. No distant metastases could be demonstrated and the lung cancer was diagnosed as non-small-cell lung cancer (poorly differentiated adenocarcinoma), tumour/node/metastasis staging (T2N3M0), stage IIIb.

Initial treatment consisted of analgesics, fluid restriction, and potassium supplementation. Before even radiotherapy could be initiated, there was rapid deterioration of clinical and mental status, with extreme wasting caused by a bronchopneumonia, and the patient died.

At autopsy a large (10×10×10 cm) tumour was found in the lower lobe of the left lung, infiltrating the surrounding lung parenchyma. The left pleura and subcarinal and paratracheal lymph nodes were also involved. No tumour was found outside the thorax. Microscopically, most of the lung tumour was necrotic. In the few well preserved areas, the tumour displayed a solid pattern with some isolated poorly differentiated glandular structures. The tumour cells were of a large size and contained conspicuous nucleoli. No small-cell components could be found. The tumour cells expressed the high molecular weight and low molecular weight cytokeratin markers, but no neuroendocrine markers.

Discussion

This patient with a rapidly progressive poorly differentiated non-small-cell lung cancer (poorly differentiated adenocarcinoma) presented with multiple paraneoplastic syndromes. Although some of the paraneoplastic syndromes seen in our patient are more typical of extrapulmonary tumours or of small-cell lung cancers than of non-small-cell lung cancer, there is sufficient evidence that the tumour was of pulmonary origin and was of the NSCLC type. At autopsy, no tumour tissue was found outside the thorax, confirming premortem clinical examination, including abdominal CT scan, gastric endoscopic examination and prostatic ultrasound examination. Tumour was found only within the thorax: a large left lower lobe mass, pleural metastases and mediastinal lymphadenopathies. Both on postmortem material obtained from the left lower lobe mass and on premortem material obtained from mediastinal lymph nodes (mediastinoscopy) and bronchial mucosa (bronchoscopy), the same histological type was found. The histological morphology, positivity pattern for cytokeratin, as well as the PAS positivity and the diffuse positivity for neuroendocrine markers are in favour of the diagnosis of poorly differentiated adenocarcinoma with neuroendocrine features. In none of these samples was a small-cell lung cancer component found. The absence of staining for neuroendocrine markers on autopsy material can be explained by autolysis. Necrosis also made electron microscopy examination impossible.

Each of the paraneoplastic syndromes seen in our patient has been associated with NSCLC, but this is, to our knowledge, the first case in which several of these syndromes (six in total) occurred concurrently.

Hypertrophic pulmonary osteoarthropathy (HPO) is characterized by clubbing of the fingers and toes, periostitis of the long bones, and sometimes a polyarthritis [3]. HPO is encountered most frequently in lung cancer, occurring in 12% of patients with adenocarcinoma and less frequently in other cell types [4]. With successful treatment of the underlying tumour the inflammatory symptoms and pain can go into remission.

Hyperkeratosis of the palms and soles, also called tylosis, is described in association with lung cancer, lymphoma and adenocarcinoma of the breast and stomach. It may typically precede the diagnosis of lung cancer for months or years [3].

Erythema annulare centrifugum (EAC) is characterized by arcuate, polycyclic, slightly elevated, erythematous lesions expanding slowly peripherally and clearing centrally. Lesions may persist indefinitely or resolve within a few days. EAC may or may not be related to an underlying disease. It has been reported in association with malignancy (predominantly myeloma and prostatic cancer, but occasionally also other solid tumours), but also with infection and drug intake [5].

In ectopic Cushing's syndrome the ACTH-precursor "big ACTH" is most often secreted. Plasma ACTH determinations may be misleadingly normal when ACTH is measured with immuno-radiometric assay (IRMA), which may miss paraneoplastic big ACTH secretion. High free urinary cortisol levels and a flat response of plasma cortisol to CRH (as seen in our patient) are, however, diagnostic for ectopic ACTH production [6]. The normal response of ACTH following CRH administration can be explained by the fact that paraneoplastic ACTH secretion occurs intermittently [6]. In this patient the hypokalaemia and the muscular weakness were probably due to the mineralocorticoid effect of cortisol hypersecretion.

In the absence of renal insufficiency, volume depletion, hypoadrenalism and hypothyroidism, the findings of serum hyponatraemia and hypo-osmolality associated with an inappropiate high urinary osmolality indicates the syndrome of inappropiate secretion of antidiuretic hormone (SIADH) [7]. This syndrome is typical of SCLC and is rarely if ever found in NSCLC. More recently, it has been demonstrated that the mediator of the syndrome in SCLC is either atrial natriuretic peptide (ANP) or arginine vasopressin (AVP), also known as ADH [8]. ANP levels have not been measured and, therefore, a contribution of this factor cannot be excluded.

Elevated plasma calcitonin levels have consistently been found in more than half of patients with SCLC and in a variable but lower frequency in the other lung cancer cell types. No clinical syndromes are associated with tumour production of calcitonin.

When reviewing the literature, using Medline and Index Medicus data bases, for the last 20 yrs we found only a few reports of the association of multiple (more than two) paraneoplastic syndromes in lung cancer.

The combination of: multiple dermatological lesions (palmoplantar hyperkeratosis, hyperpigmentation) and clubbing [9]; Lambert-Eaton syndrome, SIADH and peripheral neuropathies [10]; HPO, gynaecomastia and vascular disorders [11]; and of simultaneous secretion of multiple hormones (ACTH, calcitonin, ADH and melanocyte stimulating hormone) [12] have all been reported.

The actual occurrence of such cases with multiple syndromes is, however, probably underrepresented in the literature.

The occurrence of multiple endocrine and dermatological paraneoplastic syndromes together with HPO in the same patient is, however, an unusual, not yet described, presentation of lung cancer.

Each of the six paraneoplastic syndromes described here are probably due to a distinct humoral factor secreted by the tumour or an immunological phenomenon. Their concurrent occurrence probably represents a chance event. At the cellular level, several possibilities exist. Quite often lung cancers in individual patients contain multiple subtypes, each with distinct antigenic or endocrine properties. On the other hand, the undifferentiated phenotype of the cells in this patient could explain secretion of multiple hormones by individual cells. The immunohistochemical localization of several neuroendocrine markers in cells which have an adenocarcinoma phenotype further reduces the probability that an undetected small-cell component should account for the neuroendocrine features in this patient's tumour.

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