Clinical Endocrinology

Endocrine and Metabolic Manifestations of Cancer

E. J. ROSS

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Symptoms caused by malignant disease are not confined to the anatomical distortion and functional impairment of organs and tissues resulting from the presence of an enlarging tumour. It is becoming more and more apparent that many of the hitherto inexplicable and often bizarre accompaniments of cancer are the result of endocrine and metabolic activities of the cancer itself. Current views ascribe to the cancer cell the competence to synthesize polypeptides that mimic virtually all known polypeptide hormones produced by conventional endocrine organs. They are commonly referred to as "ectopic" hormones. These substances and the commoner cancers that produce them are listed in Table I.

TABLE I—Hormones Secreted by Malignant Cells, their Principal Sites of Origin, and the Chief Metabolic Abnormality of Diagnostic Significance

Hormone	Principal Cancers Concerned	Principal Metabolic (or Clinical) Abnormality
Corticotrophin ..	Bronchus (oat-cell) Pancreas (islet-cell) Thymoma Thyroid (papillary and medullary) Stomach Pancreas Ovary	Hypokalaemic alkalosis (weakness, thirst, polyuria)
α - and β -melanocyte stimulating hormone	Bronchus (oat-cell)	(Pigmentation)
Vasopressin	Bronchus (oat-cell) Duodenum Cerebellar haemangioblastoma Lymphoma, Hodgkin's disease	Dilutional hyponatraemia (drowsiness)
Parathormone	Bronchus (squamous cell) Bladder Uterus Vulva	Hypercalcaemia (vomiting, constipation, psychosis)
Thyroid-stimulating hormone	Choriocarcinoma Hydatidiform mole Embryoma of testis Bronchus	Hypermetabolism (tachycardia)
Gonadotrophin ..	Hepatoma Bronchus	Increased androgen production (precocious puberty)
Luteinizing hormone ..	Trophoblast tumour in women Teratocarcinoma Bronchus	Increased oestrogen production (gynaecomastia)
Gastrin	Pancreas (α -cell)	High gastric acidity (peptic ulceration)
5-hydroxytryptamine (serotonin)	Carcinoid of Small intestine Caecum Appendix	(Diarrhoea, abdominal cramps, cyanotic flushes)
5-hydroxytryptophan histamine	Carcinoid of bronchus	(Tachycardia, flushing, hypotension)

Clinical Syndromes

BILATERAL ADRENAL HYPERPLASIA

The production of a corticotrophin leads to bilateral adrenal hyperplasia and to the secretion of cortisol in far greater amounts than occurs in most cases of true Cushing's syndrome. Biochemical abnormalities produced by the continuous exposure to this very high plasma concentration are manifested by potassium depletion, leading to muscle weakness and wasting, polyuria and carbohydrate intolerance; and sodium retention, leading to oedema and hypertension. The classical features of Cushing's syndrome take some months to develop and the patient may die of his cancer before his appearance changes. Pigmentation is a feature of some patients, leading to a mistaken diagnosis of Addison's disease, and is due to the secretion of a melanocyte-stimulating hormone (β -MSH) as well as corticotrophin.

The clue to this syndrome is the presence of hypokalaemic alkalosis. Confirmation is obtained by high plasma concentration of 11-hydroxycorticosteroids, the loss of the diurnal variation in the level of the latter, and the loss of suppression by exogenous glucocorticoids, such as dexamethasone.

Classical Cushing's syndrome is rare in men and this carcinomatous syndrome should be suspected when Cushingoid features appear in a man in the cancer age group. Successful removal of the tumour or its irradiation will result in a remission of symptoms.

INAPPROPRIATE ANTIDIURESIS

The continued secretion of vasopressin (antidiuretic hormone, ADH) inappropriate to the body's needs leads to overhydration in both the intracellular and extracellular compartments. The resulting cerebral oedema leads to drowsiness, irritability, lethargy, mental confusion, and disorientation—and ultimately to coma and fits.

The clue to the diagnosis is the presence of hyponatraemia which is dilutional, as opposed to depletion, in type. All other plasma constituents will be diluted by the increased plasma content of water—for example, the blood urea concentration will be low (less than 20 mg/100 ml), the packed cell volume will be reduced, and the amount of water in the plasma expanded. Plasma osmolality, which depends largely on the plasma content of sodium and chloride, will also be low, but urine osmolality is high since water is being retained by the kidneys. In the absence of renal failure, urine osmolality above the plasma osmolality is presumptive evidence of excessive secretion of vasopressin.

Defective renal reabsorption of sodium, potassium, phosphate, glucose, and amino-acids and a partial defect of urinary acidification is present in many of these patients. This points to a proximal renal tubular abnormality which may improve if the primary tumour, (which is usually an oat-cell carcinoma of

the bronchus), can be successfully excised or irradiated. Another feature that will improve is the water retention, the patient passing large volumes of urine with a positive free water clearance. Since large quantities of potassium are also excreted, plasma potassium concentration will fall, necessitating the administration of potassium supplements.

HYPERCALCAEMIA

Hypercalcaemia in patients with cancer is most commonly due to the presence of osteolytic metastases in bone, leading to hypercalciuria and to hypercalcaemia if the kidney cannot excrete the excess calcium as fast as it is liberated. This is seen commonly in carcinoma of breast, lung, prostate, and kidney, and also in lymphomas, leukaemia, and multiple myeloma. The plasma concentrations of both inorganic phosphate and alkaline (bone) phosphatase tend to be raised.

The presence of hypercalcaemia with a reduced plasma inorganic phosphate concentration in a patient with a hypernephroma led Albright and Reifstein¹ to suggest that the tumour was secreting parathyroid hormone, an explanation now accepted as the cause of hypercalcaemia in patients with non-parathyroid tumours (for example, squamous cell carcinoma of the lung or carcinoma of the ovary) without demonstrable metastases in bone. Removal of the primary tumour leads to return of the plasma calcium to normal, with a secondary rise if the tumour metastasizes.²

The symptoms exhibited by these patients are those of hypercalcaemia due to any cause—namely, thirst, nocturia and polyuria due to impairment of renal concentrating ability, lethargy, hypotonia, muscular weakness, myoclonus, anorexia, vomiting, abdominal cramps, constipation, and psychosis. If relief of symptoms by radical cure of the tumour is impossible prednisolone may lower the plasma calcium concentration sufficiently to relieve symptoms; this is aided by the administration of sodium phosphate by mouth.

SPONTANEOUS HYPOGLYCAEMIA

Spontaneous hypoglycaemia occurs, of course, with either benign or malignant pancreatic beta-cell tumours which secrete insulin. The production of insulin by these tumours is not, however, "ectopic." Hypoglycaemia also occurs in patients with a variety of large (kilogram-sized) mesenchymal tumours—for example, fibrosarcomata and other sarcomata, fibromata of various tissues, mesothelioma, and also in hepatoma and adrenal carcinoma.

The presence of insulin-like activity in such patients has been reported sporadically and the cause of the hypoglycaemia is by no means certain. Suggestions have been "glucose hunger" caused by the high metabolic activity of these large tumours, the secretion of substances that release insulin from the pancreas, the inhibition of insulinase, the secretion of metabolites of tryptophan with hypoglycaemic properties, and impairment of hepatic glucose-6-phosphatase activity.

The symptoms are those of acute neuroglycopenia from any cause—namely, sweating, tachycardia, flushing, hunger pain, and drowsiness, terminating in coma and fits.

HYPERTHYROIDISM

Hyperthyroidism results from the production of a thyroid-stimulating hormone. The clinical manifestations differ from those of thyrotoxicosis. Common features are tachycardia, increased appetite, heat intolerance, polydipsia, and muscle weakness. Tremor may be present but eye signs are absent since long-acting thyroid stimulator is not involved. Both the serum protein-bound iodine level and the radioactive iodine uptake

by the thyroid are raised. Iodine uptake by the thyroid is not suppressed by the administration of tri-iodothyronine or thyroxine. The hyperthyroidism remits if the malignant disease is controlled by chemotherapy or other measures. If these measures fail, the hyperthyroidism can be controlled by anti-thyroid drugs.

ERYTHROCYTOSIS

Though usually referred to as "polycythaemia," the production of erythropoietin by tumours results in overproduction of the red cell series only. Red cell mass, haemoglobin concentration, and packed cell volume are increased and the bone marrow shows erythroid hyperplasia. Resection of the tumour reverses the haematological abnormality, whereas the administration of radiophosphorus does not.

PRECOCIOUS PUBERTY

Precocious puberty results in boys from the production of a gonadotrophin by tumours, with consequent stimulation of production of testicular androgens. The syndrome is characterized by a spurt in both height and weight and virilism, with enlargement of penis and testes, growth of pubic hair, and deepening of the voice. Plasma testosterone concentration and urinary excretion of 17-keto(oxo)steroids are increased and are not suppressed by the administration of exogenous glucocorticoid. These tumours have responded to treatment with methotrexate or radiotherapy, but the remission so produced is usually short-lived.

GYNAECOMASTIA

Gynaecomastia is found in association with a tumour producing a luteinizing hormone which stimulates production of oestrogens. It occurs in non-trophoblastic tumours—for example, of lung, liver, and adrenal cortex—as well as in trophoblastic tumours and teratocarcinomas.

GASTRIN-SECRETING TUMOURS

Gastrin-secreting tumours, which are benign or malignant alpha-cell tumours of the pancreatic islets, lead to the excessive production of hydrochloric acid and so to intractable and often multiple peptic ulceration, a syndrome named after Zollinger and Ellison, who described it in 1955.³ The syndrome also occurs in association with multiple adenomata in the thyroid, parathyroid, pituitary, and adrenal glands in various combinations, collectively known as the syndrome of multiple endocrine adenomatosis.

MULTIPLE HORMONAL SYNDROMES

The biosynthetic activity of a tumour is not necessarily limited to one polypeptide hormone. Numerous instances have now been reported of multiple hormonal abnormalities of a single tumour, usually an oat-cell carcinoma of the bronchus or islet-cell tumour of the pancreas, with their attendant clinical syndromes—for example, hypokalaemic alkalosis due to excessive cortisol production from the synthesis of corticotrophin and dilutional hyponatraemia due to the excessive production of vasopressin. Even more remarkable is an alpha islet-cell tumour of the pancreas which secreted not only glucagon, its appropriate hormone, but also gastrin, corticotrophin, melanocyte stimulating hormone, vasopressin and parathyroid hormone.

CARCINOID SYNDROMES

The typical carcinoid syndrome is associated with malignant argentaffin tumours of mid-gut derivatives—that is, small intestine, caecum, and appendix—metastasizing to the liver. It is characterized by episodes of watery diarrhoea, abdominal cramps, bronchospasm, and cyanotic flushes of the face and chest, with right-sided stenosing lesions of the heart caused by the secretion of 5-hydroxytryptamine (serotonin); 5-hydroxy-indoleacetic acid is found in the urine.

When the tumour arises from fore-gut derivatives—for example, the bronchus—the resulting syndrome is different. The episodic flush is red, and is accompanied by oedema of the face, salivation, and lachrymation. These symptoms may be accompanied by tachycardia, fever, tremor, anxiety, and hypotension. The metastases are in bone and skin rather than in the liver and the cardiac lesions are left-sided. Histamine, 5-hydroxytryptophan, and 5-hydroxytryptamine are found in the urine.

The difference between the two syndromes is that the former secrete 5-hydroxytryptamine into the portal circulation, whereas the latter secrete into the systemic circulation histamine and 5-hydroxytryptophan, lacking the decarboxylase to convert the latter into 5-hydroxytryptamine.

Embryological Aspects

Polypeptide hormones (vasopressin, oxytocin, melatonin, and various releasing factors) are produced in the hypothalamus in tissues which are of ectodermal (neural crest) origin and in the pituitary gland, thyroid, parathyroid, parafollicular cells (C-cells) of the thyroid (or the ultimobranchial body in lower animals), and pancreatic islet cells, which are of entodermal origin. Glands originating in mesodermal (nephrogenic ridge) tissue—that is, the adrenal cortex, ovary, and testis—produce steroid hormones.

Non-endocrine structures arising from entodermal tissue include the lungs, stomach, pancreas, duodenum, jejunum, and ileum. Malignancies in all these organs are sources of ectopic polypeptide hormones. Is there a cell common to all these which could be responsible for retention of the capability to synthesize these polypeptide hormones? A claim has been staked for argentaffin cells, to serve as neuroendocrine tissues scattered throughout non-endocrine derivatives of entodermal tissue.⁴ Argentaffin tissue, derived from neural ectoderm, invades the primitive alimentary tract and is ultimately diffusely distributed throughout tissues of fore-gut derivation. The distribution of silver-staining cells in these tissues is closely correlated with the ability to produce serotonin and other vasoactive amines. Likewise the distribution of silver-staining cells in the pancreatic alpha-islet cells and other fore-gut derivatives is closely linked to the ability to produce glucagon. Argentaffin cells similarly exist in the anterior pituitary gland, parathyroids, thyroid, C-cells, and pancreatic beta-cells—all conventional endocrine organs.

In a similar way, the chromaffin reaction is given by endocrine tissues of neuro-ectodermal origin that produce catecholamines—that is, in the adrenal medulla and in the sympathetic nervous system—and also by cells scattered throughout fore-gut derivatives. Chromaffin tissue is frequently found in association with argentaffin tissue, as in the parafollicular cells (C-cells) of the thyroid and in the carotid and aortic bodies.

These anatomical relationships are of great interest in the light of the existence of various familial endocrine syndromes—for example, the association of medullary carcinoma of the thyroid with pheochromocytoma and neurofibromatosis. They may also be of significance in the relative frequency with which neoplasms of fore-gut origin—for example, carcinoma of bronchus and pancreatic islet cells—are involved in producing

ectopic hormones which are identical with those which originate in conventional endocrine glands also derived from entodermal anlagen.

Mechanism of Ectopic Hormone Production

Two main hypotheses have been advanced to account for the ability of cancer cells to produce what appear to be inappropriate peptides. The first supposes that the malignant cell reverts to the totipotentiality of the primitive cell and again exhibits the ability to synthesize proteins long since lost by repression of the genetic message by histones. Malignancy itself is a genetic anomaly, the cells having acquired a capacity for autonomous growth so that it is not surprising that another genetic anomaly can become manifest.

The alternative hypothesis is that the abnormality is biosynthetic rather than genetic, the cancer cell producing a vast series of polypeptides some of which, by chance, possess the amino-acid sequence requisite for a known (and measurable) biological activity. Other peptides produced by cancers, of course, may have biological activity which we do not recognize as such, because we cannot measure it.

Neurological Complications of Cancer

Neurological complications of cancer are common and often disabling. They include encephalopathies, myelopathies and neuropathies, and myasthenic syndromes. Dementia may accompany carcinomatous encephalitis or cerebellar degeneration, occurring in patients without cerebral metastases. The most frequent neurological complications encountered in a patient with cancer are mixed peripheral neuropathy or a myopathy or a mixed syndrome. The distribution of the myopathy is central, with symmetrical wasting and weakness of the muscles of both limb girdles so that the patient has difficulty in rising from a low chair and mounting stairs. In some instances there is an element of myasthenia, with abnormal sensitivity to muscle relaxants.

The cause of carcinomatous encephalopathy and neuro-myopathy is at present unknown. It is tempting to ascribe it to a

TABLE II—Other Manifestations of Cancer

Complications		Neoplasms Commonly Concerned
Neurological	—myopathy —polymyositis myasthenia dermatomyositis —neuropathy—sensory mixed sensori-motor encephalopathy myelopathy	Bronchus Breast Cervix Ovary Colon
Dermatological	—acanthosis nigricans ichthyosis hypertrichosis dermatitis herpetiformis herpes zoster (dermatomyositis)	Lymphomas Breast Stomach Uterus Ovary
Vascular	—thrombophlebitis arterial thrombosis	Pancreas Ovary Cervix Breast Hypernephroma
Haematological	—leukoerythroblastic and leukaemoid reactions eosinophilia red cell aplasia erythrocytosis intravascular coagulopathy	Breast Prostate Thymus Hypernephroma
Proteinopathies	—hypoalbuminaemia hyper γ_2 globulinaemia amyloidosis eryofibrinogenaemia	Most cancers
Skeletal	—clubbing hypertrophic osteoarthropathy	Bronchus
Renal	—nephrotic syndrome (membranous glomerulonephritis)	

humoral cause but anti-brain antibodies have been reported in cancer patients with sensory neuropathy.⁵

Other manifestations of cancer are shown in Table II. The list ranges over a wide variety of apparently unconnected disorders, the common feature being that they occur in patients with cancer, either overt or later discovered, more frequently than is likely to occur by chance.

Many are relatively minor, but some give rise to disabling symptoms in their own right, in addition to those caused by the primary tumour and its metastases. Dermatomyositis, scleroderma, and polymyositis developing after the age of 40 frequently have a background of cancer⁶—particularly of breast, ovary, lung, and stomach, the breakdown products of which allegedly act as allergens.⁷ Less specific skin manifestations of cancer include pigmentation, itching, pruritus, ichthyosis, and acanthosis.

Skeletal changes are common manifestations of cancer. The cause of clubbing of fingers and toes in association with lung neoplasms has been the subject of controversy for decades and is still unresolved. Hypertrophic pulmonary osteoarthropathy sometimes accompanies clubbing and both disappear rapidly with removal of the primary tumour in the lung. Another important and painful manifestation of cancer is venous thrombosis, which is by no means confined to patients with carcinoma of the pancreas, being common in lung cancer. It appears to be due to hypercoagulability resulting from excessive circulating antihemophilic globulin or a similar factor. Arterial thrombosis may also have a background of cancer, especially hypernephroma. Intravascular coagulation may also occur.

An overlap with diseases usually regarded as being of immunological aetiology is seen in the association of Hashimoto's thyroiditis and membranous glomerulonephritis with cancer.

Incidence of Systemic Manifestations

The prevalence of the complications of cancer discussed above is not known but it has become clear that they exist much more commonly than is generally realized and will be recognized only if they are thought of and diligently pursued. Neurological abnormalities are frequent and the incidence naturally is higher in series reported by neurologists than by others, whereas endocrine and metabolic abnormalities are found most commonly by endocrinologists. Wilkinson⁸ reports an overall incidence of neuromyopathy in 14% of patients with cancer of the lung and in 16% of those with cancer of the ovary. Hormonal syndromes are also common in carcinoma of the lung: 2% of 100 consecutive admissions had adrenal hyperplasia, 2% had inappropriate antidiuresis, and 1% had hypercalcaemia.⁹ Review of a necropsy series by Azzopardi, Freeman and Poole¹⁰ showed a 6% incidence of hypercalcaemia (not further elucidated) in carcinoma of the bronchus but a lower incidence of endocrinopathies, perhaps because they were unrecognized in life.

Diagnostic Implications

Awareness of the large number of systemic abnormalities occurring in patients suffering from cancer should lead to the suspicion that unexpected and unexplained symptoms or signs or biochemical abnormalities in an individual patient may be

manifestations of a malignancy which has not yet made its presence felt in the conventional manner. The finding of dilutional hyponatraemia or hypokalaemic alkalosis should draw attention to the possibility of bronchial carcinoma, for example, or hypercalcaemia to carcinoma of the breast or erythrocytosis to hypernephroma.

These metabolic and other abnormalities may appear long before the more typical manifestations of cancer appear. For example, myasthenia had been present in a patient for three years before a haemoptysis led to a chest x-ray film, revealing a bronchial carcinoma. The reader's attention is drawn to the article "In search of a cancer" as an example of a long search for the cause of gynaecomastia in a young man aged 22.¹¹

Effect on Prognosis

Endocrine, metabolic, or other abnormalities developing in the course of a malignant disease will contribute new signs and symptoms which may add to the patient's suffering. They may also substantially alter the prognosis. Thus hypercalcaemia can add the disturbing symptoms of thirst, polyuria, nausea, vomiting, intestinal colic and constipation, and psychotic behaviour, and may prove fatal in its own right.

Of great interest is the effect of bilateral adrenal hyperplasia and the resulting high circulating concentration of cortisol on the spread of metastases. This has been noticed in animals with induced neoplasms where the pattern of neoplastic spread was altered by the administration of cortisol. A similar phenomenon occurs in patients with carcinoma of the bronchus where secondary deposits appear in unusual sites—for example, in the spleen. Cortisol appears to act as a spreading factor for cancer, perhaps by weakening the body's immunological defence mechanisms. Survival is much reduced in most patients with this complication of cancer. When it occurs in patients with cancer of good prognosis—for example, medullary carcinoma of the thyroid—consideration should be given to adrenalectomy to slow down the rate of progression of the malignancy.

Any discussion of this topic can be concerned only with metabolic aberrations that can be measured or which give rise to recognizable clinical abnormalities. Very probably cancers also produce substances—polypeptides or otherwise—which impair the functioning of normal but not of malignant cells and which are responsible for the cachexia of the patient with malignant disease and which are responsible for his ultimate demise even though all his vital organs are apparently intact.

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