Paraneoplastic syndromes

Loretta Sweeney
Theresa Howe

Abstract

Malignancy may uncommonly present with a paraneoplastic syndrome rather than as a direct result of the primary tumour or its metastases. Paraneoplastic syndromes are a heterogeneous group of syndromes that represent the non-metastatic systemic effects of malignant disease. Pathogenesis varies among syndromes but several humoral and immune mediators are implicated. Although some syndromes are rare, they can be very specific for an underlying malignant diagnosis. Recognition of the syndrome, treatment of the malignancy and supportive measures for the paraneoplastic syndrome may improve morbidity and mortality.

Keywords Neoplastic antibodies; paraneoplastic endocrine syndromes; paraneoplastic neurological syndromes; paraneoplastic syndromes

What's new?

- The vaptans, which are V2/vasopressin receptor antagonists, have now reached oncological clinical practice
- Their administration needs to be tightly monitored to avoid rapid overcorrection of sodium concentrations
- The main adverse effects include thirst and dry mouth
- Particular caution needs to be exercised in those with underlying liver disease.

Introduction

Malignancy may present with a paraneoplastic syndrome (PNS) in up to 40% of patients with specific cancers.[1] This heterogeneous group, classified according to the organ system affected, represents the non-metastatic systemic effects of malignant disease. Presentation varies widely, ranging from non-specific cachexia to pathognomonic syndromes, for example: Bazex's syndrome. A PNS presentation may significantly predate a diagnosis of malignancy.[2] This overview will discuss endocrine, neurological and dermatological PNS; it will not cover rheumatological, haematological or renal presentations.

Pathogenesis

Endocrine PNSs have been shown to result from the production of functional hormones, peptides and/or cytokines by tumour cells.[3]

Neurological PNSs arise by immune-mediated mechanisms. Normal immune function results in the generation of anti-tumour antibodies and anti-tumour-specific T lymphocytes. Certain tumours, however, ectopically express neuronal antigens that are usually exclusively found in the nervous system. It is the cross-reactivity with these which has been hypothesized to result in neurological symptoms.[4]

The pathogenesis of other categories of PNS has largely yet to be elucidated.

Endocrine paraneoplastic syndromes (Table 1)

Syndrome of inappropriate antidiuretic hormone (SIADH) secretion: this is commonly found in small cell lung cancer. In patients with SIADH with no identifiable cause, it is mandatory to do a chest X-ray. Resultant serum hyponatraemia may be an incidental finding or present with symptoms ranging from postural hypotension to confusion and seizures.

Hyponatraemia usually resolves within weeks of starting anticancer therapy. It can respond to fluid restriction, but this is challenging for the patient and sometimes ineffective. Pharmacological treatments include demeclocycline (blocks the renal action of ADH) and specific (V2) vasopressin receptor antagonists known as vaptans.[5] In severe acute cases, intravenous hypertonic sodium chloride may be required.

Cushing's syndrome: resulting from ectopic adrenocorticotrophic hormone, corticotrophin-releasing factor or cortisol production, this often presents before the associated cancer is diagnosed. It is associated with primary lung malignancies. The onset can be rapid, with associated cachexia. Patients may present with hypokalaemic metabolic alkalosis. The diagnosis of ectopic secretion is confirmed by the high-dose dexamethasone suppression test, imaging (including computed tomography of the thorax/abdomen/pelvis) and tumour markers. Bilateral inferior petrosal sinus sampling may be necessary to definitively exclude a pituitary source.

Neurological paraneoplastic syndromes (Table 2)

These can predate diagnosis of a cancer by weeks or years. The presence of certain onconeural or paraneoplastic antibodies aids diagnosis, but not all syndromes have detectable antibodies. Paraneoplastic antibodies can attack the central or peripheral nervous system and the neuromuscular junction. Magnetic resonance imaging, positron emission tomography, cerebrospinal fluid examination and electrophysiology may aid diagnosis. Treatment of the malignancy can result in an improvement or resolution of symptoms, unless permanent damage to non-

Loretta Sweeney *MBBCh MRCP FRCR is an ST7 Clinical Oncology Trainee currently OOP completing the Cutting Edge Radiotherapy Fellowship, Velindre Cancer Centre, Cardiff, South Wales, UK. Competing interests: none declared.*

Theresa Howe *MBBCh BMedSci MRCP FRCR is a Clinical Oncology Consultant with an interest in breast cancer at Velindre Cancer Centre, Cardiff, South Wales, UK. Competing interests: none declared.*

Endocrine paraneoplastic syndromes

Syndrome	Hormone/hormone-like peptide	Clinical features	Specific management	Associated malignancy
SIADH	ADH	Anorexia and nausea Malaise Confusion ↓ Serum sodium ↓ Serum osmolality ↑ Urine sodium ↑ Urine osmolality	Fluid restriction Demeclocycline Vaptans	SCLC CNS primary or metastases
Cushing's syndrome	ACTH CRF Cortisol	Pigmentation Muscle weakness Hypertension Hyperglycaemia Oedema	Ketoconazole Metyrapone Octreotide	SCLC Carcinoid MTC GI carcinomas
Hypercalcaemia	PTHrP Rarely PTH Rarely vitamin D	Nausea and vomiting Pain Weight loss Constipation Depression	Fluids Bisphosphonates RANKL antibodies Calcitonin	Many, including: Breast NSCLC Prostate Myeloma Lymphoma
Hypocalcaemia	Calcitonin	Perioral paraesthesias Tetany	Replace calcium	MTC
Hypoglycaemia	Insulin	Confusion Coma Seizures	Glucose Corticosteroids Glucagon Octreotide	Insulinomas Mesothelioma GI carcinomas Sarcomas
Carcinoid syndrome	Serotonin Kallikrein Histamine	Diarrhoea Bronchoconstriction Paroxysmal flushing Heart failure	Octreotide	Carcinoid

ACTH, adrenocorticotrophic hormone; ADH, antidiuretic hormone; CNS, central nervous system; CRF, corticotrophin-releasing factor; GI, gastrointestinal; MTC, medullary thyroid carcinoma; NSCLC, non-small cell lung carcinoma; PTH, parathyroid hormone; PTHrH, parathyroid hormone-releasing hormone; RANKL, receptor activator of nuclear factor kappa-B ligand; SCLC, small cell lung carcinoma; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Table 1

repairable critical nervous tissue has occurred. Early use of immunomodulatory therapy (corticosteroids, immunoglobulins, plasma exchange) has a role.[6]

Dermatological paraneoplastic syndromes

Acanthosis nigricans: this presents as velvety, hyperpigmented plaques often affecting flexure creases. It is strongly associated with insulin resistance. However, florid presentations in atypical sites such as palmar or plantar locations strongly suggest malignancy.[7] Patients tend to have unintentional weight loss. Gastric adenocarcinoma is the underlying malignancy in approximately 50% of malignancy-associated acanthosis nigricans.

Bazex's syndrome (acrokeratosis paraneoplastica): this is a rare phenomenon, always associated with underlying malignancy.[7] It is mandatory to investigate the aerodigestive tract for squamous cell carcinoma. It typically presents with a symmetrical psoriasiform hyperkeratotic eruption affecting the nose, ears and digits but can involve the limbs and trunk. It is associated with alopecia and psoriasiform nail changes.

Erythema gyratum repens: this is strongly suggestive of malignancy. It is usually, but not exclusively, caused by lung adenocarcinoma.[7] Concentric, often pruritic, migrating erythematous rings cover a large proportion of the body.

Necrolytic migratory erythema: this is associated with glucagonoma (pancreatic α-cells) and only occasionally with extrapancreatic malignancy.[8] This wet eczematous skin condition is often associated with constitutional symptoms of anorexia, cachexia and venous thromboembolism.

Dermatomyositis: this is associated with varied malignancies including breast, gynaecological, gastrointestinal tract and lungs.[9] There is a proximal myopathy with an erythematous skin rash, periorbital heliotrope rash, Gottron's papules and periungal telangiectasia. ◆