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Review

Paraneoplastic syndrome associated with gynaecological malignancy: a review of the evidence

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Key content

- Paraneoplastic syndrome (PNS) is a clinical manifestation of both benign and malignant tumours. Symptoms are not attributable to direct organ involvement of the cancer nor as a therapeutic adverse effect; instead, they are a result of hormones, cytokines or growth factors released by the tumour, or an immunological response.
- Paraneoplastic syndromes can affect any body system, so can cause myriad potential symptoms. These clinical manifestations often pre-date those of the underlying disease process.
- The incidence of PNS attributable to gynaecological tumours is increasing, resulting in considerable morbidity in those affected.
- There is an overall lack of awareness of PNS among clinicians; this, combined with wide-ranging signs and symptoms, creates an opportunity for diagnostic difficulty and therapeutic delay.

Learning objectives

- To raise awareness among clinicians to aid earlier diagnosis and treatment of paraneoplastic syndromes.

Keywords: cancer / diagnostic imaging / gynaecological oncology surgery / palliative care

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Introduction

Classically, the symptoms of neoplastic disease can be attributed to organ involvement or local mass effect exerted by the primary tumour or its metastases. However, many oncology patients often display symptoms that cannot be explained by such a mechanism. This phenomenon was first reported in the literature in 1888, with the disease entity eventually being labelled as 'paraneoplastic syndromes' by Guichard et al. in 1949.[1,2]

Today, paraneoplastic syndrome (PNS) is defined as a clinical manifestation of a tumour process, not resulting from direct organ involvement, metastatic disease or an adverse effect of treatment. It can affect any body system, thus encompassing myriad clinical symptoms, which – in many instances – may pre-date the diagnosis of the underlying tumour. PNS may arise from any tumour of gynaecological origin, both benign (mature ovarian teratomas) and malignant. Ovarian and endometrial malignancy are well-recognised causes of PNS. The incidence of PNS is expected to rise in conjunction with the sharply increasing incidence of endometrial cancer, attributable to the obesity epidemic of the developed world. While not exhaustive, the common causes of each PNS are outlined in Table 1.

In the UK, over 21 000 women are diagnosed with gynaecological malignancy each year. The prevalence of mature ovarian teratomas is less distinct as many women may be asymptomatic; however, we can assume this number is significant. The incidence of PNS in all oncology patients is reported at approximately 8%; however, given diagnostic difficulties, this is potentially a considerable underestimate and does not include PNS associated with benign disease.[3]

Although the phenomenon of PNS is well-recognised in literature, a lack of awareness among clinicians, combined with wide-ranging symptomatology, often means the diagnosis is delayed or missed.

In this review, we outline that the consequences of PNS are as wide ranging as they are debilitating. It is hoped a greater awareness of this condition might lead clinicians to give it more consideration in the management of these patients, thereby allowing earlier diagnosis and treatment.

Table 1. Paraneoplastic syndromes with examples of causative underlying pathology

PNS	Commonest underlying malignancy
Cushing's syndrome	Neuroendocrine carcinomas
Hyperthyroidism	Gestational trophoblastic disease and struma ovarii
Hypercalcaemia	Advanced malignancy of any origin (although this is not a true PNS), small cell carcinoma of the ovary
Hyperglycaemia	Ovarian strumal carcinoid
Paraneoplastic cerebellar degeneration	Ovarian and endometrial carcinomas
Paraneoplastic encephalitis a) Neuronal nuclear (e.g. anti-Hu) b) Neuronal surface (e.g. NMDAR)	 a) Ovarian carcinoma b) Ovarian teratomas
Dermatomyositis	Ovarian cancer

Abbreviations: NMDAR = *N*-methyl-*D*-aspartate receptor; PNS = paraneoplastic syndrome

Pathophysiology

The pathophysiology of PNS depends on the underlying tumour subtype, with the tissue of origin being an important determinant of the ensuing syndrome. Broadly speaking, the development of PNS has been attributed to two underlying mechanisms: PNS associated with an immunological response to malignancy, or with products secreted by the tumour.

Malignant growths can both secrete and upregulate homeostatic production of hormones, growth factors or cytokines, with clinical symptoms depending upon the secretion involved. For example, hyperglycaemia has been observed secondary to somatostatin production (inhibiting insulin release) by an ovarian strumal carcinoid.[4] Malignant neoplasms may also trigger a host anti-tumour immune response. Antibodies produced lack the selective ability to target only malignant cells, resulting in various autoimmune pathologies, including neurological, cutaneous, musculoskeletal and renal sequelae.

PNS is also well recognised to occur secondary to benign ovarian pathology in the form of ovarian teratomas. Ovarian teratomas may be classified as mature or immature based on their histological characteristics and malignant potential, with mature teratomas regarded as benign neoplasms.[5,6] Although benign, teratomas arise from pluripotent primordial germ cells and, as such, can contain functioning endocrine tissue.[7] This ectopic production of hormones can give rise to PNS.

Neurological paraneoplastic syndrome

Paraneoplastic cerebellar degeneration

Paraneoplastic cerebellar degeneration (PCD) manifests in those with an underlying malignancy as worsening pancerebellar symptoms over a subacute period.[8] Patients may complain of poor balance, visual disturbances (characteristically oscillopsia) and slurred speech.[8] Signs such as nystagmus, poor coordination and difficulty in walking heel-to-toe may be seen on examination.[8–10]

The commonest type of PCD is associated with the anti-Yo antibody. This group accounts for 50% of all PCD cases and, of these, 90–98% of patients will have a cancer identified.[8] In women, ovarian and breast cancers are the commonest underlying pathologies, with vaginal melanomas being a rare causative entity.[8–10] The anti-Yo antibody has been found in 23% of women with a diagnosis of ovarian carcinoma, with approximately half of these patients displaying the clinical manifestations of PCD.[8] As seen with other PNS, paraneoplastic symptoms may pre-date those of malignancy. In fact, most anti-Yo PCD cases have onset of neurological symptoms a median of 5 months prior to identification of a tumour.[9]

By its action, the anti-Yo antibody results in dysregulation of cellular calcium homeostasis, ultimately causing an increase in intracellular calcium that leads to activation of cell death pathways.[8] Anti-Yo also targets CDR2, a protein highly expressed in Purkinje cells, which is responsible for regulating transcription.[8,9] It is these mechanisms that account for the cerebellar degeneration and resulting neurology characteristic of PCD.

The diagnosis of PCD requires acute development of a severe pancerebellar syndrome in the absence of atrophic changes demonstrated on magnetic resonance imaging (MRI).[8] A paraneoplastic antibody panel should be performed to detect anti-Yo antibodies. However, these antibody titre levels do not correlate with disease severity and monitoring of titres is not recommended.[9] Given the strong correlation between anti-Yo PCD and underlying malignancy, if this diagnosis is made without the presence of a known tumour mass, further consideration should be given to the possibility of an underlying malignancy, and investigations performed to exclude the same.

Treatment options for PCD are limited to management of the underlying malignant cause, with surgical removal of the tumour load providing the most definitive treatment.[8,11] Multidisciplinary rehabilitation can restore physical function

and the ability to carry out activities of daily living.[12] However, the prognosis of this group of patients remains poor; the median survival of patients with ovarian carcinoma and anti-Yo antibody PCD is 22 months.[8]

Paraneoplastic encephalitis

Paraneoplastic encephalitis encompasses multiple neuropsychiatric syndromes, occurring secondary to neoplastic processes. They may affect any part of the central or peripheral nervous system, so can result in various clinical manifestations, ranging from behavioural changes to complex seizures. Paraneoplastic encephalitis can be further subdivided into two broad groups based on the location of the antigen against which the causative antibody is directed:

- Antibodies directed against intracellular neuronal proteins
- Antibodies directed against neuronal surface antigens

Accurate differentiation of the antibodies involved is important to both direct treatment and serve as a prognostic indicator. These antibodies can be detected in both blood and cerebrospinal fluid. It is therefore important to carry out sampling from both in the diagnostic work-up. Imaging of the brain should also be considered; although often unremarkable in such cases, imaging will aid the exclusion of other differential diagnoses.[13–15]

1. Antibodies directed against intracellular neuronal proteins (antineuronal nuclear antibodies)

This subset of paraneoplastic encephalitis results from antibodies directed against intracellular neuronal proteins. The commonest example of this is the anti-Hu antibody. These are described as 'well characterised' owing to their strong association with particular underlying pathologies. This subgroup of paraneoplastic encephalitis tends to carry a worse prognosis as there is typically a poor response to treatment.

Anti-Hu antibodies are most often associated with small cell lung cancers; however, they have been reported in association with ovarian and cervical malignancies.[16] The typical result of this interaction is a paraneoplastic limbic encephalitis, but it can also cause additional signs of brainstem pathology, cerebellar disorder and pure sensory neuropathy.[17]

2. Antibodies directed against neuronal surface antigens

The antibodies responsible for this subtype of paraneoplastic encephalitis target neuronal cell surface proteins, including receptors. The most notable antibody in this group is the *N*-Methyl-*D*-Aspartate Receptor (NMDAR) antibody, which has particular relevance to gynaecologists. NMDAR antibody encephalitis is a disease of young women, with median age at onset of 22 years.[15] It is most often seen in patients with mature ovarian teratomas and is quoted as making up 65% of cases.[18] Ovarian teratomas may ectopically express the NMDAR.[14,15,18] This ectopic expression results in an immune response to the receptor, which is then misdirected towards the neuronal antigens.[15]

NMDAR-antibody encephalitis is a progressive neuropsychiatric disorder that was first described as a paraneoplastic disorder in 2007.[18] The initial symptoms of NMDAR-antibody encephalitis resemble a viral illness, with headache and fever in 70% of patients.[14,15] Ninety-five percent of patients then develop nonspecific psychiatric symptoms and most will present to psychiatrists in the first instance.[15,19] Neurological features follow, including dystonic movement disorders, seizures and autonomic dysregulation resulting in tachycardia, hypertension and hypersalivation.[14,15]

Diagnostic work-up should include both cerebrospinal fluid and serum sampling, as antibodies may be found in one but not the other. Given the strong association with underlying ovarian pathology, tumour surveillance, in the form of ultrasound imaging, should be carried out.[14]

As the antibodies in NMDAR-antibody encephalitis have a direct pathogenic effect, their removal through immunotherapy is effective, with over 75% of patients having good neurological outcomes.[14,15] This may take the form of methylprednisolone, plasmapheresis or intravenous immunoglobulin. If untreated, NMDAR-antibody encephalitis has a severe neurological morbidity and a quoted mortality of 15%.[14] As with all PNS, early removal of any underlying tumour burden provides the most definitive treatment option

Endocrine paraneoplastic syndrome

Endocrine paraneoplastic syndromes are caused by peptides, steroids or hormones released by a tumour, which ultimately interfere with homeostasis and lead to a deranged metabolic state. These biologically active substances derive from an ectopic source (the tumour) and not the typical organ of origin; as such, the resulting syndromes are termed 'paraneoplastic'. It is important to emphasise that a hormone-secreting malignancy, derived from the usual endocrine tissue of origin of that hormone, would not be a paraneoplastic syndrome. Endocrine paraneoplastic syndromes are usually derived from endocrine or neuroendocrine neoplastic tissue.[21] Resulting syndromes include Cushing's syndrome, hypercalcaemia of malignancy and hyperthyroidism.

Cushing's syndrome

Paraneoplastic Cushing's syndrome results from ectopic production of adrenocorticotrophin hormone (ACTH) and, rarely, corticotrophin-releasing hormone (CRH), leading to excessive glucocorticoid production. Most cases (50–60%) are attributed to neuroendocrine lung tumours; for example, small cell carcinoma.[3] Importantly, ectopic ACTH and, rarely, cortisol secretion has been observed, resulting from

gynaecological neuroendocrine tumours, endometrial adenocarcinomas and ovarian teratomas.[22–24] Symptoms are the classic Cushingoid phenotype, which may or may not be accompanied by electrolyte disturbance (hypokalaemia). These clinical findings may pre-date those of malignancy, with the underlying neoplasm being found in the diagnostic work-up. Diagnosis is confirmed by elevated circulating cortisol and ACTH and failure of cortisol to be suppressed by dexamethasone. Management of paraneoplastic Cushing's syndrome requires strict regulation of electrolyte disturbances and prompt reduction of hypercortisolaemia in the form of surgical resection of the underlying neoplasm.

Hypercalcemia

Malignancy-associated hypercalcaemia has an incidence of 30% in all oncology patients.[25] It can result from all tumour subtypes. It is most often found in disseminated disease, so tends to be a poor prognostic factor. Most reports in the literature quote a 30-day mortality rate of 50% for patients with malignancy-associated hypercalcaemia.[26] It can be a result of bony metastatic disease associated with increased osteoclastic resorption of bone; however, as outlined earlier, this would not fall under the umbrella of a true paraneoplastic syndrome. Specifically, paraneoplastic hypercalcemia refers to elevated circulating calcium secondary to parathyroid hormone related protein (PTHrP) secreted by the tumour (humoral hypercalcemia of malignancy), causing renal calcium retention and increased osteoclast activity.[25] This is commonly seen in gynaecological oncology, particularly with clear cell carcinomas and small cell ovarian carcinomas.[27] Small cell carcinoma of the ovary, hypercalcaemic type (SCCOHT) is a highly aggressive tumour subtype typically diagnosed in young women. It is a rare entity in the general population, seen in less than 1% of ovarian malignancies, but is strongly associated with deleterious germline and somatic mutations in SMARCA4. It carries an extremely poor prognosis, even when confined to the ovary at the time of diagnosis.[28,29] Paraneoplastic hypercalcemia is seen in most cases.[30]

Classic complaints of hypercalcaemia include pain caused by resorption of bone, renal failure, constipation and abdominal discomfort, central nervous system disturbance and behavioural changes.[31] Laboratory investigations demonstrate hypercalcaemia, raised PTHrP and normal-to-low PTH levels. Hypercalcaemic patients will be dehydrated at baseline owing to hypercalcaemia-induced nephrogenic diabetes insipidus, on top of probable poor oral intake associated with the symptoms mentioned earlier. The mainstay of initial treatment is aggressive fluid rehydration. This is combined with pharmacological attempts to lower serum calcium using bisphosphonates.[25] Ultimately, surgical resection of the underlying tumour burden is pivotal to the definitive treatment of malignancy associated hypercalcaemia.

Hyperthyroidism

Hyperthyroidism is defined by elevated circulating levels of thyroid hormone. Again, paraneoplastic hyperthyroidism refers specifically to ectopic production of either thyroid hormone or a stimulant of thyroid tissue. This is seen with two particular gynaecological malignancies: struma ovarii and gestational trophoblastic disease (GTD).

Struma ovarii (ovarian goitre) is a variant of an ovarian teratoma, specifically with thyroid tissue constituting greater than half of the overall teratoma. It accounts for 2.7% of all dermoids.[32,33] While most struma ovarii are benign, thyroid-type malignancies – most often papillary carcinoma – may arise within this subgroup of ovarian teratomas. Most cases of struma ovarii present as any other mature teratoma, with a similar age of presentation. Ascites, presenting as an atypical Meigs syndrome, may be seen in one-third of cases.[6] Hyperthyroidism complicates 5% of cases because of the ectopic thyroid tissue functioning to secrete thyroid hormones.[34] As such, thyroid function tests should be monitored once the diagnosis of struma ovarii is considered. Diagnosis is confirmed by radioactive iodine uptake seen in the pelvis. Treatment takes the form of antithyroid drugs and, ultimately, surgical resection. In cases of a functional struma ovarii, surgery carries a significant risk of thyroid storm. Careful use of antithyroid drugs, combined with adequate analgesia and, ideally, a laparoscopic approach, is required in the pre- and perioperative periods to prevent this, with cessation of these drugs and thorough postoperative monitoring.[35]

Gestational trophoblastic disease (GTD) is a spectrum of conditions ranging from a molar pregnancy through to its malignant form: choriocarcinoma. Persistence of GTD is referred to as gestational trophoblastic neoplasia. Gestational choriocarcinoma most often arises from a hydatidiform mole or following termination of pregnancy, but can also follow a normal pregnancy. The incidence of choriocarcinoma is 1 per 66 775 live births, which rises with both paternal and maternal age.[37] Choriocarcinomas are composed of mononuclear cytotrophoblasts and multinucleated syncitiotrophoblasts. It is these primitive placental cells, especially syncitiotrophoblasts, which are responsible for the characteristically high levels of human chorionic gonadotrophin (hCG). The molecular structure of the alpha subunit of hCG (αhCG) mimics that of thyroid-stimulating hormone (TSH). Homeostasis is maintained with moderate rises in hCG (as seen in pregnancy) by downregulating pituitary production of TSH. However, the high circulating levels of hCG seen in GTD may cause excessive stimulation of TSH receptors, leading to clinical hyperthyroidism. Thyroid stimulation, and therefore thyrotoxic symptoms, are directly proportional to the level of hCG. The potency of hCG to stimulate the receptors is 4000 times less than TSH, thus explaining why such high levels of hCG are needed to result in hyperthyroidism.[38] Thyroid function is seen to normalise with treatment of the choriocarcinoma. This takes the form of single or multiple agent chemotherapy, depending upon disease stage (Table 2) and risk stratification. The World Health Organization (WHO) has

Table 2. International Federation of Gynecology and Obstetrics (FIGO) anatomical staging of gestational trophoblastic neoplasms[36]

FIGO stage	Description
Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus but is limited to genital structures (adnexa, vagina, broad ligament)
Stage III	GTN extends to the lungs, with or without known genital tract involvement
Stage IV	All other metastatic sites

developed a risk score to enable consideration of prognostic factors other than disease stage, allowing a more individualised approach to treatment (Table 3).[36,39,40]

Rheumatological paraneoplastic syndrome

Dermatomyositis

Dermatomyositis is an autoimmune inflammatory myopathy with associated cutaneous manifestations. Incidence is twice as common in females, classically having a bimodal age distribution creating two subsets: juvenile and adult dermatomyositis. Adult dermatomyositis is attributable to paraneoplastic phenomena in 25% of cases, with ovarian cancer being the commonest underlying pathology.[41–43] The musculocutaneous symptoms of this PNS often precede the typically nonspecific symptoms of ovarian malignancy. Bilateral, progressive, proximal muscle weakness, in association with cutaneous manifestations, such as a periorbital rash and Gottrons papules are pathognomonic of dermatomyositis. These clinical manifestations are a result of autoimmune complexes targeting skin and muscle antigens. While the treatment of dermatomyositis is largely medical (corticosteroids and immunosuppressive agents), gynaecologists should be aware of the association with underlying ovarian malignancy to allow appropriate tumour surveillance.

Conclusion

The prevalence of all cancers among an ever-ageing population is rising. Gynaecological malignancies, in particular endometrial cancer, have seen a sharp increase in incidence, an observation directly attributable to the obesity epidemic of the developed world. As the number of oncology patients rise, the incidence of PNS rises in correlation. Gynaecological malignancy is no exception, providing a significant contribution to the numbers suffering from PNS. These syndromes result in considerable morbidity in an already challenged population. Greater awareness of paraneoplastic syndromes should allow earlier consideration of PNS in those with diagnosed malignancy, but also raise awareness of the possibility of an underlying tumour in those presenting with paraneoplastic signs and symptoms. Raising the index of suspicion among clinicians facilitates earlier diagnosis and management in this cohort of women.

Table 3. International Federation of Gynecology and Obstetrics (FIGO) scoring system for gestational trophoblastic disease, by prognostic factor[37]

	FIGO stage			
Parameter	**0**	**1**	**2**	**4**
Age (years)	<40	≥40	-	-
Previous pregnancy	Mole	Abortion	Term	-
Months since last pregnancy	<4	4–6	7–12	>12
Pretreatment hCG (IU/L)	<10	10^3–10^4	10^4–10^5	>10^5
Number of metastases	0	1–4	5–8	>8
Site of metastases	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Largest tumour mass (cm)	-	3–5	>5	-
Previous chemotherapy	-	-	Monotherapy	Combined therapy

Total score: ≤6 = lower risk of resistance to treatment
Total score: ≥7 = high risk of resistance to treatment. Abbreviations: hCG = human chorionic gonadotrophin

Disclosure of interests
There are no conflicts of interest.

Contribution to authorship
IH instigated and edited the article. AB researched, wrote and edited the article, with contributions from DF. SM contributed to editing the article. All authors approved the final version.

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