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Review article

What to expect from paraneoplastic syndromes of the nervous system in uterine cancer: A review of the literature

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ABSTRACT

Neurological paraneoplastic syndromes are a rare subgroup of diseases commonly related to neuroendocrine tumors. However, they have been associated with uterine malignancies (sarcomas, endometrial carcinomas, and neuroendocrine cancers). Their presentation often correlates with a cancer diagnosis or cancer recurrence underlining their clinical significance. The most common neurological paraneoplastic syndrome in uterine cancer is cerebral degeneration with a comprehensive clinical presentation of pancerebral dysfunction. However, other neurological syndromes present with various symptoms leading to delayed diagnosis. Less common paraneoplastic neurological syndromes associated with uterine cancer are encephalitis, encephalomyelitis, subacute sensory neuropathy, sensory-motor neuropathy, dermatomyositis, cancer-associated retinopathy, opsoclonus, Guillain-Barre syndrome, necrotizing myopathy, and stiff-person syndrome. Herein, we reviewed published cases of neurological paraneoplastic syndromes in uterine cancer in order to raise awareness of these rare syndromes. We recorded patients' clinical presentation, antibodies detected, treatment, and clinical outcomes.

1. Introduction

Uterine cancer is the most common gynecological malignancy in developed countries. Its clinical symptoms, mainly abnormal uterine bleeding, are well known, attributing to a timely diagnosis by a suspecting clinician. However, its rare correlation with paraneoplastic syndromes leads to differential diagnosis problems and belated diagnosis.

Paraneoplastic neurologic syndromes are a diverse group of disorders with a variety of clinical presentations mediated mainly by cross-reacting immunological mechanisms. They affect less than 1 % of cancer patients, primarily those with neuroendocrine tumors. Their appearance prior to diagnosis or tumor recurrence complicates the diagnosis and should elicit a prompt search for an underlining malignancy. To facilitate the diagnosis of these rare neurological syndromes, the 2021 guidelines define neurological paraneoplastic syndromes as disorders that affect any part of the nervous system, are cancer-associated, and specific neuronal antibodies support their immune-mediated pathogenesis (Graus et al., 2021).

This review aims to raise awareness of these rare neurological syndromes by presenting clinical cases of women with uterine cancer.

2. Methods

This review's search strategy and data abstraction were performed per the PRISMA guidelines. Eligible articles were identified by searching the MED-LINE bibliographical database up to December 10th, 2021. The used keywords were: "(paraneoplastic) AND (endometrial cancer OR uterine) AND (neurological)." All studies written in English that included patients with uterine cancer and a neurologic paraneoplastic syndrome were eligible. In addition, we checked all the references of retrieved articles in order to identify additional potentially eligible articles. Only the most recent guidelines were included. Forty papers were selected to be included, and 8 more were added to aid the spheric presentation of these case reports. In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

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3. Paraneoplastic syndromes of the nervous system

In gynecological cancers, paraneoplastic syndromes usually complicate epithelial ovarian and breast cancer. Cerebral degeneration is the most common neurological syndrome reported in gynecological malignancies. Common paraneoplastic antibodies found in gynecological malignancies include anti-Ri, anti-Ta, anti-amphiphysin, and ANNA-1 (anti-Hu) (Bi et al., 2006). However, in uterine cancer, paraneoplastic syndromes of the nervous system are extremely rare and limited in some case reports.

3.1. Cerebral degeneration

Paraneoplastic cerebral degeneration (PCD) is an uncommon syndrome associated with uterine carcinomas. Its clinical presentation is of pancerebral dysfunction, with patients developing dizziness, nausea, and vomiting, progressing to instability, ataxia, diplopia, nystagmus, dysarthria, and dysphagia. PCD is caused by marked degeneration of Purkinje cells and inflammation in the cerebral cortex, deep cerebellar nuclei, and the inferior olivary nuclei due to the crossed reaction of antibodies responding to neural antigens expressed by the tumor (Dalmau and Rosenfeld, 2008; Karpathiou et al., 2016). The anti-Yo (PCA-1) is the most common paraneoplastic antibody and the one primarily associated with gynecological malignancies, while anti-Tr, anti-Hu (ANNA-1), anti-Ri (ANNA-2), anti-CRMP5 (CV2), anti-Ma1, anti-Ma2 (Ta), anti-Recoverin, anti-Amphiphysin, anti-GAD, and anti-SOX1 are less common (Tanriverdi et al., 2013; Graus et al., 1991; Panegyres and Graves, 2012). Diagnosis of the syndrome primarily presupposes ruling out other more common causes of such symptoms (metastatic spread of cancer, metabolic and toxic causes, neurogenerative or infectious diseases). Almost 40 % of cases do not have detectable antibodies (in the CSF or serum), underlining that diagnosing paraneoplastic syndromes can rely on the patient's clinical course.

Clinical presentation of patients with PCD and an underlining uterine tumor does not differ from other malignancies (Karpathiou et al., 2016; Liontos et al., 2021; Lie et al., 2016; 2016.). A 70-year-old endometrial cancer patient from our cancer center presented with a rapidly progressive cerebral syndrome, anti-Yo antibodies in the serum confirmed the diagnosis, while the CSF analysis, as well as the MRI and CT scans, were not pathognomonic (Liontos et al., 2021). The clinical course of the syndrome can be devastating as treatment with immunosuppressants or chemotherapy for the underlining malignancy is of limited benefit as part of the neurological damage is irreversible, leaving the patients with various degrees of permanent disabilities (Karpathiou et al., 2016; Liontos et al., 2021; Erez et al., 2007). Furthermore, PCD has been described as an indicator of cancer recurrence (Lie et al., 2016; 2016.) and its diagnosis in a known cancer patient should elicit a prompt search for a progression of their disease (Brock et al., 2001; Johns et al., 1999; Rana et al., 2012; Gliem et al., 2011).

3.2. Encephalitis and encephalomyelitis

Paraneoplastic encephalitis is a rare occurrence in uterine cancer and can present with a diverse array of symptoms depending on the part of the brain affected. It is associated with various onconeural antibodies (anti-Hu, Ma2-associated, anti-CRMP5, anti-Ri, anti-KLHL1) usually detected in neuroendocrine tumors. Diagnosis requires extensive imaging and serological testing along with lumbar puncture and electroencephalography (EEG) in order to exclude other more common causes of neurological symptoms.

Anti-Hu antibodies or ANNA-1 (antineuronal nuclear antibodies) are shown to be directed against neuronal-specific RNA-binding proteins involved in neuronal development and maintenance. They are most commonly associated with SCLC producing a variety of clinical presentations like subacute sensory neuronopathy, limbic encephalitis, paraneoplastic cerebellar degeneration, and rarer ones like man-in-a-barrel syndrome (Gozzard and Maddison, 2010). As with other paraneoplastic syndromes, its diagnosis commonly predates cancer, and imaging studies do not usually show abnormalities (Dalmau et al., 1992).

More specifically, limbic encephalitis has been reported in a patient with uterine cancer (Côté-Mantha and Savard, 2012). The diagnosis preceded that of uterine cancer and was based on the neurological syndrome (Table 1) and the presence of anti-Hu antibodies in the patient's serum. Moreover, encephalomyelitis in a uterine leiomyosarcoma patient with anti-Hu antibodies has been described as coinciding with her disease progression and marking a dismal clinical course (Duff et al., 2006).Furthermore, temporal lobe epilepsy is a possible paraneoplastic syndrome in an anti-Yo (+) endometrial cancer patient (Petit et al., 1997).

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis has also been described in uterine cancer patients with large-cell neuroendocrine, uterine endometrioid carcinoma (Kobayashi et al., 2017) and poorly differentiated neuroendocrine carcinoma (Hara et al., 2011). The patient's clinical presentation was in line with known Anti-NMDAR encephalitis symptoms, and anti-NMDAR antibodies were found in the CSF fluid analysis (Table 1) (Kobayashi et al., 2017). NMDAR encephalitis is only about 5 % associated with an underlining malignancy, yet the infrequency of the syndrome should not disqualify its diagnosis.

3.3. Paraneoplastic subacute sensory neuronopathy

Paraneoplastic subacute sensory neuronopathy (PSSN) results from the immune response to the onconeural antigens expressed by the tumor. Immune response affects the dorsal root ganglia provoking sensory loss, ataxia and autonomic dysfunction. The prognosis is poor as the T cell response produces irreversible damage in the ganglia. It is again associated with tumors with neuroendocrine differentiation and anti-Hu or anti-collapsin-responsive mediator protein 5 (CRMP5) antibodies (Antoine et al., 2001; Graus et al., 2001).

Its correlation with uterine cancer has also been shown in patients with mixed mullerian tumors with neuroendocrine differentiation presented with the syndrome (Table 1) (Bi et al., 2006; Fournier et al., 2013). Anti-Hu antibodies were found in the serum, confirming the PSSN diagnosis, and despite the patient receiving treatment for the underlining tumor and immunosuppressive therapy, no signs of neurological recovery were detected.

3.4. Sensory-motor neuropathy

Paraneoplastic polyneuropathy is prevalent among cancer patients but rarely affects uterine cancer patients. The most common type of sensorimotor neuropathy described in endometrial carcinoma is vasculitic sensorimotor polyneuropathy presented as a severe asymmetrical sensorimotor deficit with proximal motor weakness receding after tumor treatment and immunosuppression (Vasku et al., 2011).

Paraneoplastic peripheral neuropathy with predominately motor manifestations has also been reported in uterine cancer with a disease course parallel to the underlining malignancy. (Yamada et al., 1988). Interestingly, in the needle electromyogram (EMG), there was a decrease in the quantity of discharge, polyphasic potentials, along with high-amplitude potentials, while in the autopsy, axonopathy was considered the driving process of this paraneoplastic syndrome. A predominantly axonal neuropathy with little segmental demyelination–remyelination and no signs of vasculitis was also found in a 77-year-old woman with an endometrioid endometrial carcinoma (ECC) presenting with a mixed neuropathy (Durmus et al., 2010). These cases, inherently different from known paraneoplastic syndromes like PSSN and vasculitic sensorimotor polyneuropathy without known antineuronal antibodies, highlight the wide range of the paraneoplastic neurological syndromes.

Table 1
Summary of syndromes.

Paraneoplastic syndrome	Tumor pathology	Clinical presentation	Antibodies detected	Treatment options	Outcome
Cerebral degeneration (Karpathiou et al., 2016; Panegyres and Graves, 2012; Liontos et al., 2021; Lie et al., 2016; 2016.; Erez et al., 2007; Brock et al., 2001; Johns et al., 1999; Rana et al., 2012; Gliem et al., 2011)	EEC, USC, Carcinosarcoma, Clear cell carcinoma, poorly differentiated adenocarcinoma	dysarthria, dysmetria, ataxia (truncal, cerebellar), proximal muscle weakness, bilateral dysdiadochokinesis, bilateral intention tremor, pyramidal features, nystagmus, blurry vision, abnormal extraocular movements, hypophonic speech, titubation, vomiting, vertigo, dysphagia	Mostly anti-Yo (+) in serum and/or tumor tissue and/or CSF	Tumor resection, Adjuvant chemotherapy, IVIg, Corticosteroids, plasmapheresis, medroxyprogesterone acetate, primidone, propranolol, gabapentin, pregabalin, topiramate	Stable disease or minimal clinical improvement but mostly rapid progression of symptoms and death in 8–10 months
Encephalitis (Côté-Mantha and Savard, 2012; Petit et al., 1997; Kobayashi et al., 2017; Hara et al., 2011)	EEC, Neuroendocrine carcinoma, Carcinosarcoma	epilepsy, retrograde amnesia, hallucinations, psychosis, delusions, oral automatism, restricted eye movements, orofacial dyskinesias, hearing impairment, vertigo, facial numbness, pain and paresis, visual blurring, cognitive slowing, man-in-a-barrel syndrome, signs of meningeal irritation, coma	Anti-Yo in serum, Anti-Hu in serum, Anti-NMDAR in CSF and/or in primary cancer site and/or in serum	Chemotherapy, Tumor resection, plasmapheresis, IVIg corticosteroids, cyclophosphamide	Mild motor improvement up to death of tumor progression or multiorgan failure within 3–18 months
Encephalomyelitis (Duff et al., 2006)	Leiomyosarcoma	Dysphagia, peripheral sensory neuropathy, hemifacial spasm, epilepsy, dysphagia, dysarthria	Anti-Hu in serum	Corticosteroids, plasmapheresis	Acute deterioration and death in 6 weeks
Paraneoplastic Subacute sensory neuropathy (Fournier et al., 2013)	Malignant mixed mullerian tumor	Imbalance, sensory loss, areflexia, truncal and appendicular ataxia, BP fluctuations	Anti-Hu in serum	Chemotherapy, IVIg, corticosteroids, plasmapheresis	Severe disability to rapid deterioration and death
Sensorymotor neuropathy (Yamada et al., 1988; Durmus et al., 2010)	EEC, poorly differentiated	Muscle weakness, progressive numbness, ataxia, wide-based gait, Romberg's sign	–	Tumor resection, corticosteroids, pregabalin	Slight improvement to death within 4 months
Dermatomyositis (Lim et al., 2020; Wada et al., 2014; Kasuya et al., 2013)	EEC	Erythemato-violaceous plaques on face, upper chest, back, arms and fingers, heliotrope rash, Gottron papules, muscle weakness, intermittent fever	– Anti-TIF1γ in serum, Anti-p155/140 antibody, TIF1γ-overexpressing malignant neoplasm	Tumor resection, Tumor resection, chemotherapy, corticosteroids	Improvement of symptoms but recurrence with disease progression
Cancer-associated retinopathy (Hoogewoud et al., 2018)	Uterine sarcoma	Subacute visual loss and visual field constriction, photosensitivity, ring scotomatous visual field loss	–	Plasmapheresis, corticosteroids, azathioprine, cyclosporine	Improved intraocular inflammation
Opsoclonus (Lewis et al., 2010)	USC	Vertiginous sensation, bouncing vision, opsoclonus	–	Tumor resection	Radical improvement
Guillain-Barre syndrome (Tho et al., 2006)	EEC	Symmetrical bilateral weakness, sensory loss, dysarthria, deterioration in respiratory function	–	IVIg	Gradual improvement
Stiff person syndrome (Yeoh et al., 2020)	Not specified	Numbness, weakness, urinary and fecal incontinence.	Anti-GAD	Unknown	Unknown

3.5. Dermatomyositis

Dermatomyositis (DM) is an idiopathic inflammatory myopathy presenting with proximal skeletal muscle weakness, evidence of muscle inflammation, and various cutaneous manifestations. Up to 9.4 % of DM cases are associated with an underlying malignancy. This is based on the temporal relationship between cancer diagnosis and DM and its improvement or relapse parallel to that of malignancy (Yang et al., 2015). Specific serum antibodies, namely anti-TIF1γ, anti-NXP2, and anti-p155 autoantibody, are associated with positive cancer risk (Lu et al., 2014), with anti-TIF1γ having a significant negative predictive value for the diagnosis of cancer-related myositis. In that light, an annual cancer screening for 3–5 years is strongly recommended for DM patients with cancer-associated autoantibodies (Lim et al., 2020).

Darosa et al. reported a case of anti-nuclear antibodies and anti-TIF1γ positive DM diagnosed by skin biopsy (Lim et al., 2020). Simultaneously the patient was diagnosed with metastatic endometrial adenocarcinoma and, within 7 days of the tumor surgery, exhibited a rapid improvement in their skin manifestations. The correlation between the clinical course of the two diseases indicates the paraneoplastic nature of the dermatomyositis in this case and in other cases reported (Wada et al., 2014; Kasuya et al., 2013; Orth et al., 1999).

3.6. Cancer-associated retinopathy

Cancer-associated retinopathy (CAR) is the most common paraneoplastic visual syndrome, yet rare, even more so in uterine cancer. It is characterized by diffuse retinal degeneration caused by a mainly B cell-mediated cross-reacting autoimmune response to retinal antigens. Antibodies correlated with CAR are targeted against alpha-enolase, transducin-alpha, carbonic anhydrase II, and most commonly recoverin (Adamus, 2009). However, no antibodies are detected in many cases, highlighting the possible role of both cellular and humoral immunity. Timewise it can preside or coincide with the cancer diagnosis. As the retinopathy can affect both cones and rods, its clinical presentation can vary with photosensitivity, ring scotomatous visual field loss and attenuated retinal arteriole caliber being a classical triad. In a report on a uterine cancer patient, fluorescein angiography revealing periphlebitis and papillitis and OCT with atrophy of the outer retinal layers with foveal sparing helped diagnose the syndrome, while electroretinogram

(ERG) can also be abnormal. Patients can be treated with a combination of plasmapheresis, systemic corticosteroids, azathioprine, and cyclosporine to improve their intraocular inflammation (Hoogewoud et al., 2018).

3.7. Opsoclonus

Opsoclonus is a disorder of ocular motility defined by spontaneous, involuntary, arrhythmic, conjugate saccadic eye movements, usually observed within the frame of opsoclonus-myoclonus ataxia. Patients often develop truncal ataxia and gait difficulties, while brainstem and cerebellar signs and encephalopathy may follow, leading to substantial impairment (Bataller et al., 2001). It is best described in SCLC and pediatric neuroblastomas, and it is probably associated with the presence of anti-neuronal antibodies (Armangué et al., 2016). There have been reports of anti-Ri, anti-Hu, and other paraneoplastic antibodies; however, adult opsoclonus patients are most commonly seronegative for well-characterized antibodies (Bataller et al., 2003).

Lewis et al. reported a patient with a mixed endometrial adenocarcinoma presenting with vertigo without tinnitus or hearing loss, normal funduscopy, and negative serum paraneoplastic autoantibody panel (Lewis et al., 2010). The progressive resolution of most symptoms after tumor surgery suggests an underlying antibody-mediated mechanism. Furthermore, researchers mention symptom alleviation as a response to immunotherapy (corticosteroids, cyclophosphamide, IVIG) or even high doses of clonazepam (Bartos, 2006).

3.8. Guillain-Barre syndrome

Guillain-Barre syndrome (GBS) is the most common subacute polyneuropathy with a variety of clinical presentations. The most frequent one is rapidly ascending paralysis that may involve the upper limbs, cranial nerves and can cause respiratory impairment. Inflammatory demyelination is caused by both humoral and cell-mediated mechanisms triggered by molecular mimicry to peripheral nerve epitopes (Willison, 2005). A similar mechanism has been hypothesized in paraneoplastic GBS though the lack of serum and CSF markers highlights the need for further investigation. Paraneoplastic GBS is rare but has been associated with lymphomas, leukemias, breast and colon cancer.

Tho et al. presented a case where a woman with uterine adenocarcinoma showed rapidly progressing symptoms compatible with an acute demyelinating neuropathy diagnosis (Table 1) (Tho et al., 2006). Imaging studies did not produce abnormal results, and the lumbar puncture showed an elevated protein content. The significant temporal correlation with the patient's malignancy explained the paraneoplastic nature of the syndrome.

Interestingly, frequently paraneoplastic GBS is associated with cancer treatment (Christodoulou et al., 2004) as its immunosuppressive state is hypothesized to enhance the immunologically mediated demyelination. Such a relation between cancer treatment and GBS can complicate the diagnosis due to the high frequency of chemotherapy toxicities, underlining the importance of the clinician's awareness of the syndrome.

3.9. Stiff person syndrome

Stiff-person syndrome (SPS) is a rare disorder of the nervous system, distinguished by progressive muscle stiffness, rigidity, and painful axial muscle spasms leading to severely impaired mobility and abnormal spinal posture. It is defined by heightened muscle activity resulting from glutamic acid decarboxylase (GAD) blockade, usually mediated by anti-GAD antibodies, however, in most paraneoplastic SPS cases, anti-GAD antibodies are not present (McKeon et al., 2012) and the syndrome is linked to anti-amphiphysin, anti-gephyrin, and anti-Ri antibodies (Grimaldi et al., 1993). A report by Yeoh et al. introduces a 53-year-old patient with anti-GAD (+) SPS diagnosed with endometrial cancer one year after the syndrome's diagnosis (Yeoh et al., 2020). The patient exhibited mild yet progressive symptoms and was treated with opioids. Typically, patients with paraneoplastic SPS have been shown to respond to tumor excision and glucocorticoid treatment, implying the functional rather than the structural nature of CNS alterations of the syndrome.

4. Discussion

4.1. Summary of main results

According to our search, paraneoplastic neurologic syndromes in uterine cancer rarely occur with just 27 case reports found in the bibliography. These clinical entities along with their presentation, paraneoplastic antibodies detected, treatment, and outcomes, are summarized in Table 1. Cerebral degeneration is the most reported syndrome, with a patient also diagnosed in our center.

No specific pattern between the histological types of the disease and the presence of paraneoplastic syndromes was noted in the cases summarized in this literature review. However, as depicted in Table 1, ECCs constitute a minority of the cases despite being the most frequently diagnosed histology among uterine cancer patients (Talhouk et al., 2015).

4.2. Results in the context of published literature

Paraneoplastic neurologic syndromes in uterine cancer are a very diverse group of disorders. Patients' clinical presentation often includes an array of symptoms that can mislead the physician and delay the diagnosis. The infrequency of their association with uterine cancer also contributes to this delay, as more common conditions are usually responsible for patients' neurologic presentation.

The timing of the syndromes' diagnosis is also of importance. Patients frequently develop neurologic paraneoplastic syndromes before cancer diagnosis or disease progression. In that light, imaging studies and testing for known paraneoplastic antibodies in a patient with a rapidly progressing neurologic syndrome should be discussed.

Regarding the biology of these entities, it is unknown whether the development of neoantigens that trigger autoimmune reactions is mediated by specific molecular events (McGranahan et al., 2016). The diversity of histological types associated with specific paraneoplastic syndromes indicates that this is probably not the case. Many uterine cancer patients have either POLE mutations or Microsatellite Instability High (MSI-H) tumors (Talhouk et al., 2015) that underlie the generation of multiple mutations and could predispose to developing neoantigens that trigger paraneoplastic syndromes. Unfortunately, these data are missing for the presented cases and further molecular characterization of cases is needed to support such a hypothesis.

4.3. Strengths and weaknesses

Due to the rarity of these syndromes, the small number of patients reviewed can obscure the pleomorphism of their clinical presentation. Furthermore, relevant data considering the molecular characterization of tumors are missing from some cases hindering a better understanding of the biology of these syndromes.

This study aims to raise awareness of these scarcely occurring syndromes. By presenting these cases comprehensively, including their clinical presentation, treatment used and clinical outcome, these rare entities are made easier to recognize by the clinician. To our knowledge this is the first study that organizes the paraneoplastic neurologic syndromes in uterine cancer patients.

4.4. Implications for practice and future research

Prompt diagnosis of paraneoplastic neurological syndromes is of utmost importance due to their rapidly evolving clinical course. As

shown by case reports, treatment possibilities are limited and aim at treating the underlying malignancy with the proper anticancer therapy and secondarily at controlling the autoimmune reaction using immunomodulatory agents. However, the neurological consequences are often irreversible, and patients' symptoms remain stable or continue to progress.

Finally, paraneoplastic syndromes are indicative of antitumor immunological activation and could serve as a model to understand resistance mechanisms to immune surveillance that could facilitate novel treatment development in these patients. The use of immunecheckpoint inhibitors is controversial as may lead to the exacerbation of the neurological symptoms while proven efficacy is limited.

5. Conclusion

To conclude, a physician must acknowledge, detect and diagnose a paraneoplastic neurologic syndrome, however rare, as prompt treatment can dramatically change a patient's outcome. Likewise, diagnosing such a syndrome should lead to a comprehensive search for a possible underlining malignancy.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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