Neurologic Complications of Female Reproductive Tract Cancers

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Introduction

Malignancies of the female reproductive tract can cause direct and indirect complications on the central and peripheral nervous system. Direct effects include malignant cell infiltration of the brain, spinal cord, nerve roots and plexi, and peripheral nerves, as well as compression of surrounding structures by the tumor itself or regional lymph nodes. With the exception of choriocarcinoma, gynecologic cancers, however, are regarded as "neurophobic" due to their low metastatic potential to the central nervous system (CNS). The most common gynecologic tumors to cause CNS metastases are chorio-, ovarian, and endometrial carcinoma. Indirect effects of gynecologic cancers include paraneoplastic syndromes, particularly paraneoplastic cerebellar degeneration and anti-NMDA receptor encephalitis, and complications of cancer treatment, such as chemotherapy-related peripheral neuropathy, surgery-induced peripheral nerve, and radiation-induced plexopathy. This chapter reviews the epidemiology, clinical features, treatment, and prognostic data of some of the most common metastatic, paraneoplastic, and treatment-related complications of gynecologic cancers.

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Nervous System Metastases from Gynecologic Cancers

Choriocarcinoma

Choriocarcinomas are classified under the category of gestational trophoblastic diseases (GTDs) . All types of GTDs arise from placental trophoblastic tissue after normal or abnormal fertilization [1]. They are grouped into hydatidiform moles (also known as "molar pregnancy" and subclassified into complete and partial hydatidiform moles) and gestational trophoblastic neoplasia (GTN; subclassified into invasive moles, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor) [2]. Choriocarcinoma is the most aggressive type of GTN, due to its propensity for early vascular invasion and widespread metastasis, and causes CNS metastases in up to 40% of patients [3]. Although most cases of choriocarcinoma are gestational (i.e., arising from a normal or abnormal pregnancy), a non-gestational form also exists, which can be of gonadal (e.g., ovarian or testicular) or extragonadal origin (e.g., the pineal body, mediastinum, and retroperitoneum) [4].

The incidence of choriocarcinoma varies greatly with geographical location. According to the National Cancer Institute, the estimated incidence in the USA is 2–7 per 100,000 pregnancies [5], similar to incidence ratios in Europe, Australia, some areas of Latin America, and the Middle East [1]. In Asia, the incidence ranges from 5 to 12 per 100,000 in Japan and 63–202 per 100,000 in Thailand, India, Indonesia, and China [1]. These wide ranges are partly attributed to differences in reporting and diagnostic criteria. The two best established risk factors for choriocarcinoma are extremes of maternal age (<20 years, >40 years) and previous molar pregnancy [1]. The latter increases the risk of a subsequent one to 1%. With two or more previous molar pregnancies, this risk further increases to 25% [1, 6]. Most choriocarcinomas occur after a molar pregnancy but they can also be preceded by a normal term pregnancy, abortion, or ectopic pregnancy [4].

Histopathologically, choriocarcinoma is characterized by highly invasive and vascular masses of cytotrophoblasts and syncytiotrophoblasts without villi surrounded by necrosis and hemorrhage [1]. Human chorionic gonadotrophin (hCG) produced by malignant cells is characteristically elevated and serves as a tumor marker for diagnosis, monitoring of treatment response, and posttreatment surveillance [1, 6].

Classically, patients present with abnormal uterine bleeding. In addition, a rapidly enlarging uterus, pelvic pain, and signs of hCG overstimulation, including hyperemesis gravidarum, pre-eclampsia, and hyperthyroidism may be elicited. The most common sites of metastases are lung (80%), vagina (30%), brain (10%), and liver (10%) [7]. Patients may come to medical attention due to symptoms related to metastatic rather than primary disease such as dyspnea, cough, vaginal bleeding or purulent discharge, neurologic symptoms, jaundice, and epigastric pain [8]. Work-up of suspected choriocarcinoma should include pelvic examination, quantitative measurement of serum hCG, pelvic ultrasound, thyroid, liver, and renal function tests, and chest X-ray due to the high risk of pulmonary metastases. Further evaluation with CT of the chest, abdomen, and pelvis and brain MRI may be necessary if the initial work-up or clinical presentation is concerning for metastatic disease [8].

Choriocarcinoma is staged according to a combined system defined by the International Federation of Gynecology and Obstetrics (FIGO) and World Health Organization (WHO). The former includes the conventional anatomic staging criteria, whereas the latter incorporates a prognostic scoring system of eight variables that predicts response to single-agent chemotherapy (CHT) with methotrexate (MTX) and actinomycin D: age, antecedent pregnancy, interval from index pregnancy, pretreatment serum hCG level, largest tumor size (including uterus), site and number of metastases, and prior CHT [8]. Patients can be stratified as "low risk" (score 0–6) or "high risk" (score $\geq$ 7), which predicts low versus high resistance to single-agent CHT, respectively, and the need for multiple chemotherapeutic agents [8].

CNS metastases typically cause symptoms of increased intracranial pressure (ICP) , including headache, vision changes, nausea, vomiting, tinnitus, and altered mental status [8–10]. Other manifestations are hemiparesis and seizures, the latter being particularly common with cortically-based lesions. In addition to the standard aforementioned work-up, brain MRI with and without contrast is the diagnostic study of choice for CNS metastases [8]. The most common presentation is intracerebral hemorrhage, due to invasion of blood vessels by chorionic villi [10]. The diagnosis of metastatic choriocarcinoma should thus be considered in any woman of reproductive age with a hemorrhagic brain lesion. Endovascular metastases can also lead to formation of cerebral aneurysms with subsequent rupture [11–14] (Fig. 26.1a–f) as well as arterial [15] and venous infarctions [16]. Spinal and epidural metastases are very rare [17–19].

Human chorionic gonadotropin levels can vary dramatically in metastatic CNS disease, ranging from <500 to >500,000 mIU/ml [9, 10, 20]. Given the high risk (70–100%) of concurrent lung involvement with CNS metastases [9, 10, 20–22], CT chest should be routinely performed as part of the work-up [8]. The rate of concurrent renal and liver metastases is lower, ranging from 12 to 19% [10, 20, 21]. Pelvic ultrasound is helpful to detect uterine involvement and identify those who may require hysterectomy [8].

Systemic CHT forms the cornerstone of treatment of metastatic choriocarcinoma and consists of MTX- and actinomycin D-based therapies. The most widely accepted approach is EMA-CO (etoposide, MTX, and actinomycin D, alternating weekly with cyclophosphamide and vincristine) or, in those with concurrent metastatic liver disease, EMA-EP (etoposide, MTX, and actinomycin D, alternating weekly with etoposide and cisplatin). The dose of MTX is lower (1 g/m^2) than that commonly used in other types of CNS malignancy such as primary CNS lymphoma (3.5–8 g/m^2), but higher than for metastatic choriocarcinoma to other systemic sites [20]. In those with a high burden of CNS disease or significant systemic involvement at the time of CNS diagnosis, low-dose etoposide and cisplatin can be administered before definitive treatment with EMA-CO/EP [20]. The duration of therapy varies among practitioners. The Charing Cross group recommends treatment until serum hCG levels have normalized, followed by consolidation for eight additional weeks thereafter [20, 21]. Others have given shorter courses of EMA-CO/EP (as few as two cycles) and EMA only as consolidation therapy (up to six cycles) [22]. In addition, dexamethasone should be administered to reduce cerebral edema.

The routine use of surgery, radiotherapy (XRT), and intrathecal (IT) CHT is controversial. Craniotomy with surgical resection of solitary or superficial metastases can prevent hemorrhage, relieve mass effect, and improve neurologic outcome. Whole-brain radiotherapy (WBRT) at 2000–3000 cGy (in fractions of 200–300 cGy) has been used at some centers with systemic EMA-CO/EP [9, 10]. However, the benefit of WBRT plus systemic CHT over systemic CHT alone is not clearly established. Some argue that the addition of WBRT results in disease remission if CNS disease is diagnosed at the time of clinical presentation ("early" disease) but not if it develops during active treatment with CHT or after an initial complete or partial response to treatment ("late" disease) [10]. In one case series [10], three of four patients with "early" disease achieved remission after WBRT plus EMA-CO, whereas all three patients with "late" disease undergoing the same treatment

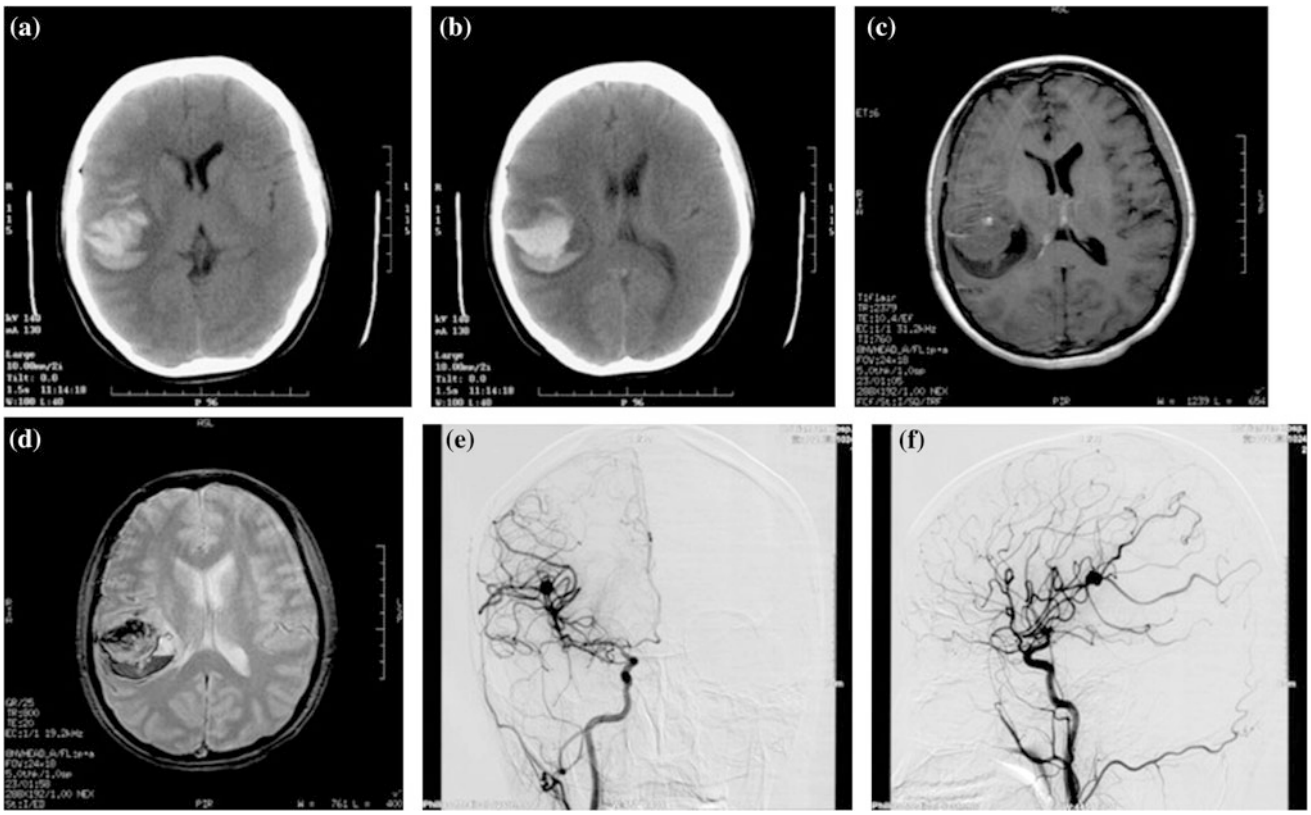

Fig. 26.1 CNS complications of choriocarcinoma. Representative images of an aneurysmal hemorrhage from choriocarcinoma. **a**, **b** CT head shows an intraparenchymal hemorrhage in the right temporoparietal lobe with mass effect. Axial T1 MR imaging (**c**) and T2-weighted MR imaging (**d**) reveals a heterogeneous lesion with blood products. **e**, **f** Cerebral angiogram demonstrates an aneurysm in the distal right middle cerebral artery. Used with permission of Elsevier from Wang et al. [11]

protocol died. This could, however, reflect the overall poor performance status and response to therapy of those with "late" disease rather than a direct effect of WBRT on survival. Given the known long-term neurotoxic sequelae of WBRT, some groups thus advocate against routine use of WBRT [20]. Instead, stereotactic radiosurgery (SRS) has assumed an increasingly important role in treating CNS metastases, particularly multiple small or unresectable lesions and after completion of systemic CHT to prevent relapse and/or treat residual disease [9, 10, 20, 21]. Lastly, IT CHT has been employed as an adjunct to systemic CHT, with the goal of achieving higher cerebrospinal fluid (CSF) drug levels. Some administer IT MTX (12.5 mg) routinely during non-EMA weeks until serum and CSF hCG levels have normalized [20, 21], whereas others [10] reserve it for patients with "late" disease. Treatment response is monitored by serial measurements of serum hCG levels, neurologic and overall clinical status, and disease burden on MRI brain.

The cure rate for metastatic choriocarcinoma is higher than that for metastatic disease from other solid tumors but reported response rates vary. The Charing Cross group observed remission in 85% of patients treated with EMA-CO/EP plus IT MTX, in the absence of WBRT [20, 21]. In another case series [9] comparing overall survival (OS) in patients treated before and after 1995, survival rates had increased from 46 to 64% but did not reach the numbers reported by the Charing Cross group. The remission rate was even lower (27%) in a cohort from the Philippines, although this was likely influenced by local confounders such as financial barriers and access to treatment [10].

The presence of neurologic symptoms at the time of presentation [9], "late" (vs. "early") disease [10], and concurrent liver metastases [21] may portend a worse outcome. Some data also suggest that a long interval from antecedent pregnancy to diagnosis of CNS metastasis is associated with poorer prognosis [23]. There is no clear established treatment protocol for those who fail to respond to EMA-CO/EP, but regimens based on etoposide and a platinum agent (e.g., cisplatin) have been used in combination with bleomycin, ifosfamide, or paclitaxel with modest success [9].

Ovarian and Fallopian Tube Cancer

Ovarian neoplasms are divided into epithelial ovarian cancer (EOC) and ovarian germ cell tumors. EOC constitutes the vast majority (95%) of ovarian malignancies and is regarded as one entity with fallopian tube and primary peritoneal cancer, given their shared embryonic origin and similarities in pathogenesis, clinical behavior, and treatment [24]. This section discusses the neurologic complications of EOC and primary fallopian tube cancer. The neurologic sequelae of ovarian germ cell tumors, specifically ovarian teratoma, are typically seen in paraneoplastic syndromes and will be discussed in a separate section of this chapter.

Ovarian cancer is the second most common gynecologic cancer after endometrial cancer and the leading cause of gynecologic cancer-related mortality [25], with a mortality rate of 7.7 per 100,000 per year [26]. The lifetime risk for a woman to develop ovarian cancer is 1.3%. The incidence is 12.1 per 100,000 [26] and highest in the developed world (Europe, USA) [24]. The most significant risk factor is family history of ovarian and breast cancer. Specifically, the presence of a genetic mutation in the *BRCA1* and *BRCA2* genes increases the risk of EOC to 39–46% and 12–20%, respectively [24]. Additional well-established risk factors are nulliparity, early menarche, late menopause, and age >50 [27]. By contrast, primary fallopian tube cancer is very rare, comprising less than 1% of all gynecologic malignancies [28]. In a Finnish study, the incidence was 5.4 per million per year [29]. Risk factors for fallopian tube cancer are less well established than for ovarian cancer, but high parity appears to be protective [29]. Most fallopian tube cancers are serous adenocarcinomas [28, 29].

Early-stage EOC often presents with nonspecific symptoms, such as anorexia, fatigue, early satiety, back pain, weight loss, nausea, vomiting, and urinary urgency and frequency. Patients rarely complain of abdominal or pelvic discomfort [24], often resulting in diagnostic delay. With disease progression, increased abdominal girth, pain, bloating, and fullness can develop [24]. About 75% of patients with EOC have stage III or IV disease at the time of diagnosis [24]. By contrast, fallopian tube cancer is rarely asymptomatic and typically presents with vaginal bleeding or spotting and abdominal pain due to tubal distension [28].

The initial step in the diagnosis of EOC is transvaginal ultrasound, which is more sensitive than CT in detecting and characterizing pelvic masses [24]. Serum CA-125 level is helpful in establishing the diagnosis as it is raised in >80% of those with advanced disease but lacks sensitivity and specificity [30]. It is also routinely used to monitor response to treatment and tumor recurrence [24, 29]. Surgical staging by exploratory laparotomy is performed in most patients and consists of total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO), examination of peritoneal surfaces, infracolic omentectomy, biopsies of pelvic and para-aortic lymph nodes, and peritoneal washings [24]. Patients with high-grade (grade 3 or higher) disease of any stage receive adjuvant CHT (a combination of a platinum agent such as carboplatin or cisplatin and a taxane such as paclitaxel or docetaxel). Individuals with stage I moderately differentiated (grade 2) cancer may also benefit from CHT [24]. The use of intraperitoneal (IP) CHT varies amongst providers due to potential problems with toxicity, drug administration, and risk of complications (e.g., intraperitoneal infections and adhesions) [24].

Local metastases involve the abdomino-pelvic-peritoneal compartment and regional lymph nodes first [24, 28]. The most common extra-abdominal metastatic sites are the pleural space (33%), liver (26%), and lung (3%) [24, 31]. Although EOC is the second most common cancer of the female reproductive tract to metastasize to the CNS, this occurrence is very rare with an incidence between <1 and 2.5% [32, 33]. Notably, these numbers may underestimate the true incidence and merely reflect symptomatic lesions, given that brain imaging is not routinely performed in ovarian cancer [33]. Given its much rarer occurrence, the incidence of CNS metastases from fallopian tube cancer is likely even lower [34].

CNS metastases can occur in isolation or in the setting of disseminated metastatic disease. Approximately, 30–44% of patients have isolated CNS relapse [32, 35, 36]. In general, CNS involvement is a manifestation of late disease that afflicts patients with prolonged survival after treatment of their systemic disease. More than 80% have stage III or IV cancer when CNS metastases are diagnosed, and most have grade III disease [35]. Figure 26.2a, b illustrates a characteristic patient with stage IIIc ovarian cancer who developed multifocal CNS involvement five years after her initial diagnosis. The median time from EOC diagnosis to CNS involvement was 21.5–46 months in different review series [32, 35], which was significantly longer than the time to development of liver and lung metastases (five and seven months, respectively) [32]. In up to two-thirds of patients, the underlying histology is of serous origin [32, 36].

In addition to parenchymal brain metastases, leptomeningeal dissemination has been described in ovarian cancer [37–39]. Although even less common than parenchymal disease, recognition and work-up of leptomeningeal involvement is important as it has significant implications for treatment and prognosis. Patients most often present with multifocal neurologic deficits, including multiple cranial nerve palsies, radiculopathy from nerve root and cauda equina infiltration, ataxia from cerebellar involvement, and signs of increased ICP secondary to hydrocephalus [40]. Contrast-enhanced MRI of the neuraxis may show

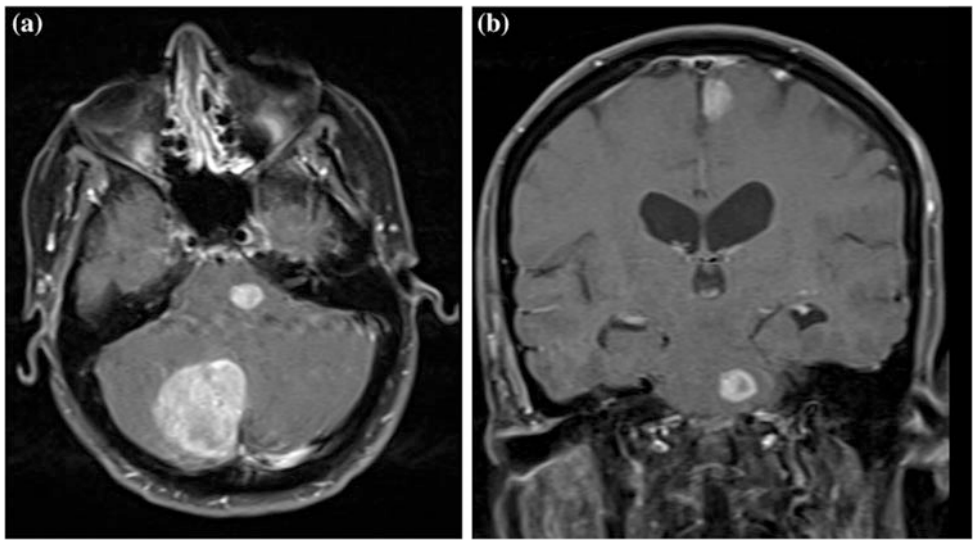

Fig. 26.2 CNS complications of ovarian cancer. Post-contrast **a** axial and **b** coronal T1-weighted MR images of a 55-year-old woman with a history of stage IIIc ovarian cancer (serous histologic subtype, *BRCA*-positive disease) who presented with headaches five years after initial diagnosis. MRI revealed parenchymal metastases in the (**a**) *right* cerebellar hemisphere, (**a**, **b**) *left upper* brainstem, and (**b**) *left frontal* lobe. CSF was positive for malignant cells. She underwent surgical resection of the right cerebellar lesion, followed by XRT to the resection cavity and residual disease. She is currently receiving IT topotecan every two months for leptomeningeal disease and is two years out from her CNS diagnosis. Courtesy of and reproduced with permission of Dr. Jose Carrillo, University of California, Irvine

enhancement in the subarachnoid space but sensitivity of imaging is low, with false negative rates ranging from 30 to 70% [40]. CSF cytology was only 71% sensitive in one study but the diagnostic yield can be increased by repeated large-volume lumbar punctures, rapid sample processing, and obtaining fluid from symptomatic sites [41]. High CSF opening pressure, pleocytosis, and elevated protein support the diagnosis of leptomeningeal carcinomatosis.

As with most parenchymal brain metastases, corticosteroids can rapidly restore neurologic function but their effects are short-lived. Median OS was two months only on corticosteroids alone [35]. In general, patients with good performance status, controlled or absent systemic disease, and a solitary and surgically accessible lesion may be good surgical candidates. In this population, prospective data have shown that surgery plus WBRT prolongs OS and reduces the rate of local relapse, compared to WBRT alone [42, 43]. Such randomized controlled data are not available for metastatic ovarian cancer specifically but a retrospective case series [44] found that resection of solitary metastases and adjuvant WBRT improved OS (23 months) compared to WBRT (5 months) or surgery alone (7 months). In an uncontrolled case series, surgery followed by either WBRT or carboplatin resulted in OS of 16 months [36]. Surgery is more difficult if multiple metastases are present. Although feasible and associated with prolonged survival (14 months vs. 3 months in those who did not undergo surgery) [45], its implementation largely depends on the anatomic location of the lesions, the patient's clinical and functional status, and expertise of the neurosurgeon.

For patients with unresectable lesions, nonsurgical candidates, or those refractory to WBRT, SRS may be an alternative option [25, 46]. SRS involves high doses of focused radiation to brain metastases, delivered either by a linear accelerator or gamma knife. The limiting factor for SRS is lesion size, and it is typically only considered for lesions <3 cm in diameter. It remains controversial whether WBRT plus SRS is superior to SRS alone [47]. Similarly, no randomized controlled trials to date have compared surgery versus SRS.

The role of systemic CHT in the management of metastatic ovarian cancer is unclear. The main disadvantage of CHT is its inability to cross the blood–brain barrier (BBB), although CNS drug penetration may partly be facilitated by a disrupted BBB as a result of metastatic disease. Systemic CHT is often administered in the presence of concurrent extracranial metastases, sometimes resulting in improved OS. Although this may merely reflect better systemic disease control rather than CNS remission, others have reported potential benefits of systemic CHT in isolated CNS disease [48, 49]. Treatment of leptomeningeal disease is largely palliative and typically consists of WBRT, IT CHT (MTX, cytarabine, thiotepa), or systemic CHT [40].

Overall prognosis for patients with parenchymal CNS metastases from ovarian and fallopian tube cancer is poor and likely significantly worse in the setting of

leptomeningeal disease. Two factors appear to consistently affect OS: performance status and presence of concurrent extracranial metastases [32, 36]. For instance, median OS was nine months in those with concurrent extracranial disease versus 21 months in those with isolated CNS metastases [36]. Prolonged survival is exceptionally rare. One patient survived for 31 months after diagnosis of multiple brain metastases from stage IV EOC and successful treatment with carboplatin but ultimately succumbed to recurrent abdominal disease [48]. Micha et al. [50] reported a patient with stage IV EOC who remained in clinical remission for 7 years after surgery and WBRT. Lastly, a small number of case reports have documented prolonged OS (range of 36–82 months) in patients with advanced-stage fallopian tube cancer [34, 51].

Endometrial Cancer

The vast majority of uterine malignancies originate from the endometrium. Endometrial carcinoma is the most common gynecologic malignancy in the developed world, with an incidence of 24.6 per 100,000 women per year and a lifetime risk of 2.7% in the USA [52–54]. In developing countries, it is the second most common gynecologic malignancy after cervical cancer. More than 75% are endometrioid adenocarcinomas and most occur as a result of excess endogenous or exogenous estrogen without opposing progestin [53]. The typical presentation is abnormal uterine bleeding in post-menopausal women and intermenstrual, heavy, frequent, or prolonged uterine bleeding in pre-menopausal women [53, 55].

At the time of diagnosis, most women (80%) have grade I and II endometrioid cancer ("type I"), which is usually estrogen-responsive and portends a good prognosis [53]. The remaining 20% have grade III or non-endometrioid cancer of other histologic origin ("type II"), including papillary serous, clear cell, squamous cell, mixed, and undifferentiated subtypes [53, 56]. Prognosis in type II endometrial cancer is less favorable, partly because it responds less robustly to estrogen-based therapy. The non-endometrioid subtypes also have a higher propensity to metastasize [53], usually via the lymphatic system to pelvic lymph nodes or by local invasion [57]. Although rare, metastases can also occur via the hematogenous route to the lungs and liver [57].

Endometrial carcinoma is staged by the FIGO and "tumor, nodes, metastasis" (TNM) surgical staging system, which incorporates various risk and prognostic factors, including histologic (FIGO) and nuclear grade, depth of myometrial invasion, involvement of the uterine cervix, and presence of local or distant metastases [53]. For disease confined to the uterus, the standard treatment is TAH-BSO with or without pelvic and para-aortic lymph node dissection [52], although conservative management may be considered in those with well-differentiated disease and lack of myometrial invasion and adnexal disease who wish to preserve fertility [56]. The use of adjuvant CHT or XRT is determined by numerous clinical and pathologic factors, including patient age and ethnicity, histologic grade, disease stage, status of peritoneal cytology, and involvement of the lower uterine segment [53]. Recurrence of disease following treatment can occur either locally or at distant sites [56].

Endometrial carcinoma is the third most common gynecologic cancer to metastasize to the brain [25, 58] but, as with ovarian and fallopian tube cancer, CNS involvement is exceedingly rare and occurs in only 0.3–0.9% of patients [59, 60]. This number increases to 3% if autopsy cases are included [61]. Tumor cells likely disseminate to the lungs first via the hematogenous route, with subsequent spread to the CNS. Factors that increase the risk of brain metastasis include certain histologic subtypes (papillary serous, clear cell, poorly differentiated tumors) and advanced surgical stage [59, 60]. Although most CNS metastases occur in the setting of widely disseminated late-stage disease, exceptions have been reported. Martinez-Manas et al. [57] treated a woman with isolated disease recurrence in the brain 1.5 years after treatment for a stage IIB papillary endometrioid adenocarcinoma. Similarly, Gien et al. [60] observed two patients with successfully treated stage IIB and IIIc endometrial carcinoma and no systemic disease who presented with multiple brain metastases two and seven months after completion of treatment, respectively. In another patient, neurologic symptoms preceded the diagnosis of an endometrioid carcinoma [60].

The reported median time between diagnosis of endometrial carcinoma and brain metastasis ranges from 0 to 52 months [58, 59, 62, 63]. Some authors have observed CNS involvement early during the disease course, especially in patients with vascular and deep myometrial invasion, thus underscoring the aggressive nature of tumors with metastatic tendency [60, 62].

Treatment recommendations for brain metastases in endometrial cancer are largely based on observational results. Similar to data from CNS metastases in ovarian cancer, surgical resection followed by WBRT is superior to surgery or XRT alone for patients with controlled extracranial disease and good performance status. In one case series of ten patients, those who underwent surgery and WBRT with or without SRS had a median OS of 15 months, compared to those who had XRT or surgery alone (median OS 2.4 and 2.7 months, respectively) [58]. Another study reported even longer OS (28 and 83 months) in two patients treated with surgery and WBRT, compared to OS of

3 months in patients receiving WBRT only [59]. For patients with multiple symptomatic brain metastases with or without uncontrolled extracranial disease, WBRT is the treatment of choice [58, 59]. The role of adjuvant CHT is less well defined but usually reserved for those with multiple brain lesions and concomitant systemic disease. One proposed regimen is four to six cycles of paclitaxel and carboplatin in addition to pelvic XRT for patients with advanced or high-risk (stage III) disease [60].

In general, prognosis is grim and median OS after diagnosis of CNS disease ranges from one to 19 months [57–60, 62, 64]. Survival may be improved in those with single compared to multiple brain lesions. For instance, two patients survived for 82 [64] and 83 [59] months, respectively, after diagnosis of a solitary brain metastasis treated with resection and WBRT.

Cervical Cancer

Cervical cancer is the third most common gynecologic cancer in the developed world, following ovarian and endometrial cancer [65]. The incidence in the USA is 7.7 per 100,000, and the estimated lifetime risk is 0.6% [66]. It has long been recognized that human papillomavirus (HPV), specifically HPV 16 and 18, is the key pathogenic driver of cervical neoplasia, being present in 99.7% of affected patients [67]. Other risk factors include early onset of sexual activity, multiple sexual partners, increasing parity, early age of first birth, low socioeconomic background, history of sexually transmitted diseases, and immunosuppression [68]. The typical clinical presentation of early disease is irregular, heavy vaginal, or post-coital bleeding, whereas pelvic or back pain can indicate advanced-stage disease [69]. Squamous cell carcinoma is by far the most common histologic subtype, followed by adenocarcinoma [68].

Most metastases from cervical cancer occur via direct local invasion or by lymphatic spread. Hematogenous spread is rare and tends to affect lungs, bone, and liver first before involving the CNS. Concurrent lung metastases have been reported in up to two-thirds of patients with CNS disease [70]. The reported incidence of metastatic CNS disease ranges from 0.4 to 1.2% [71–73]. As with ovarian and endometrial carcinoma, CNS metastases have been observed in patients of all disease stages and can occur before, during, or after completion of systemic therapy [72, 74]. Median OS with metastatic CNS disease is poor, ranging from 2.3 to 8 months [71, 72, 74, 75]. Patients undergoing surgery and adjuvant XRT tend to survive longer than those receiving either treatment modality alone [71, 72, 74, 75]. SRS alone prolonged survival to 22.5 months in one patient [72].

Paraneoplastic Diseases Associated with Gynecologic Cancers

Unlike direct malignant cell infiltration from a primary tumor, paraneoplastic syndromes (PNS) arise from an immune-mediated reaction by the host to an underlying cancer. Certain malignancies express proteins similar to those found on neuronal tissue and can trigger an immune response against these proteins, with subsequent cross-reactivity involving the nervous system. PNS can antedate the diagnosis of an underlying malignancy by months or years but also occur after a cancer has been diagnosed or during remission following cancer treatment. Of all solid tumors, small cell lung cancer (SCLC) is the leading cause of PNS, followed by breast and gynecologic malignancies [76].

The general management of PNS relies on the identification and appropriate treatment of the primary tumor (e.g., surgical resection of tumor with or without systemic CHT), immunosuppression (e.g., corticosteroids), and targeted removal of circulating onconeural antibodies (e.g., intravenous immunoglobulin (IVIG) and plasma exchange (PLEX)). Refractory cases may require treatment with a cyclophosphamide or rituximab. In some instances, long-term immunosuppression with azathioprine or mycophenolate mofetil is needed. In addition to pharmacologic treatment, physical, occupational, and speech therapy, and intensive rehabilitation should be incorporated to improve and maintain functional outcome.

Gynecologic cancers are most frequently associated with paraneoplastic cerebellar degeneration (PCD) and anti-NMDA receptor (NMDAR) encephalitis. Other PNS, including paraneoplastic peripheral neuropathies, opsoclonus myoclonus syndrome, limbic encephalitis, retinopathy, and Lambert-Eaton syndrome are rarely seen with gynecologic tumors [76, 77]. Table 26.1 provides a summary of these PNS.

Paraneoplastic Cerebellar Degeneration

Paraneoplastic cerebellar degeneration (PCD) occurs in <0.1% of gynecologic cancers [78] but is the most common paraneoplastic disease seen in reproductive tract cancers [76]. The type of underlying cancer and antibody determines the severity of symptoms, presence of other non-cerebellar features, and clinical outcome. The typical presentation is a subacute, severe, and progressive pancerebellar syndrome, with axial, appendicular, and gait ataxia, vertigo, dysarthria, and diplopia. Cognitive impairment [79] and non-cerebellar symptoms have been described. For instance, anti-Hu antibody-associated PCD can present with concomitant

Table 26.1 Paraneoplastic syndromes associated with gynecologic malignancies

Paraneoplastic syndrome	Typical onconeural antibody; gynecologic neoplasm	Treatment[a]	Prognosis
Paraneoplastic cerebellar degeneration	Anti-Yo; most commonly ovarian cancer but also fallopian tube, uterine, and cervical cancer	Corticosteroids, IVIG, PLEX Tacrolimus RTX	Poor
Anti-NMDAR encephalitis	Anti-NMDAR; ovarian teratoma	First-line: corticosteroids, IVIG, PLEX Second-line: RTX, cyclophosphamide	Good
Peripheral neuropathy	No clear antibody association; ovarian, endometrial, cervical cancer	Corticosteroids, IVIG	Variable
Opsoclonus myoclonus syndrome	Anti-Ri (weak association); ovarian and fallopian tube cancer, ovarian teratoma	Corticosteroids, IVIG Symptomatic treatment (benzodiazepines, levetiracetam, gabapentin, valproic acid, topiramate)	Variable but generally good
Limbic encephalitis, retinopathy, Lambert-Eaton syndrome	Individual cases reported with ovarian, endometrial, and cervical cancer. General treatment approach consists of corticosteroids, IVIG, PLEX, and/or immunosuppression. Guanidine and 3,4 diaminopyridine may be helpful in Lambert-Eaton syndrome. Prognosis is variable		

[a]In all cases, the underlying neoplasm should be treated

peripheral neuropathy and a brainstem/limbic encephalitis [80].

PCD is most frequently seen with ovarian, breast, and SCLC but has also been reported in association with fallopian tube, uterine, and cervical cancer [79, 81]. In most cases of PCD, the associated onconeural antibody is directed against an intracellular protein. The antibody varies depending on the underlying malignancy. In ovarian and breast cancer, there is a strong association with anti-Yo antibody (also known as Purkinje cell cytoplasmic antibody type 1 (PCA 1)) [76]. These antibodies have also been found in patients with uterine [79, 82], fallopian tube [78, 79, 82–84], cervical [76, 85], and primary peritoneal malignancy [84]. By contrast, PCD in non-gynecologic cancers is associated with anti-Hu (anti-neuronal nuclear antibody 1 or ANNA1), anti-Ri (ANNA2), and anti-Tr antibody [81]. In one case series, anti-Yo antibodies were the most frequently detected antibodies in PCD with a relative frequency of 38%, compared to lower rates of anti-Hu (32%), anti-Tr (14%), and anti-Ri (12%) antibodies [80]. Given the strong association of anti-Yo antibody with gynecologic and breast neoplasms, its presence should prompt a thorough search for underlying malignancy. Its specificity for gynecologic cancers ranges from 47 to 60% [79, 80] to >80% [76, 84, 86].

CSF studies can be normal [78] or show a lymphocyte-predominant pleocytosis, mildly elevated IgG and protein, and oligoclonal bands [79, 86, 87]. Brain MRI is usually normal in the early stages but can evolve to cerebellar or brainstem atrophy with disease progression (Fig. 26.3a, b), reflecting the histopathologic hallmark of cerebellar cortical atrophy and loss of cerebellar Purkinje cells [79, 88]. All patients with suspected PCD should undergo comprehensive work-up for underlying malignancy, including CT of the chest, abdomen, and pelvis, mammography, pelvic ultrasound, and CA125 measurement to screen for ovarian cancer [78]. FDG-PET should be considered if CT imaging does not reveal malignancy; sensitivity and specificity of FDG-PET to detect occult malignancy in PNS can be as high as 83 and 25%, respectively [89]. If initial work-up is negative, some authors advocate for repeat mammography, pelvic examination, uterine dilatation and curettage, and eventually surgical exploration of the pelvic organs [79, 86]. When an underlying gynecologic cancer is found, it is typically high grade. In one case series, most patients with a gynecologic malignancy, a clinical syndrome consistent with PCD, and positive anti-Yo antibody titers had poorly differentiated grade III cancer [84]. Interestingly, total metastatic volume was significantly smaller compared to controls with confirmed ovarian cancer and no PCD, suggesting that the autoimmune process limits metastatic spread [84].

PCD typically follows a relentless, progressive course. Neurologic symptoms tend to stabilize at the time of diagnosis and with initiation of treatment [79, 80] but neurologic recovery is rare, even with exhaustive therapy [79, 88]. In some patients, antibody titers remain elevated despite successful treatment of the underlying primary malignancy and stabilization of neurologic disease [79]. PCD associated with gynecologic cancers and anti-Yo antibodies carries a particularly dismal prognosis. In a retrospective case series of

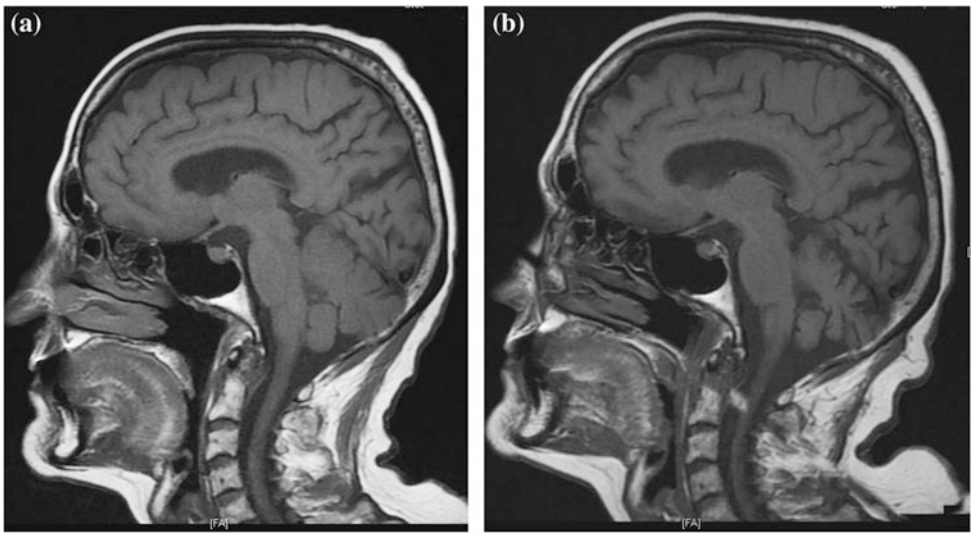

Fig. 26.3 Paraneoplastic cerebellar degeneration. Sagittal T1-weighted images of a 71-year-old woman with FIGO stage IIIc ovarian cancer (**a**, **b**). Following surgery, the patient was treated with carboplatin and taxol and several months into therapy started having some difficulty with balance. She underwent brain MRI (**a**) which was unremarkable. She was tested for presence of paraneoplastic antibodies and was found to have anti-Yo antibodies. She subsequently received several courses of IVIG without improvement. Her symptoms progressed gradually over the next two years and she developed severe ataxia and dysarthria. Her MRI 27 months after diagnosis of the ovarian cancer showed atrophy of the cerebellum (**b**)

fifty patients with PCD, 79% of those with anti-Yo antibodies were bedbound at the peak of disease, compared to <60% of those with anti-Tr and anti-mGluR1 antibodies and 17% of those with anti-Ri antibody [80]. The same study also showed a trend toward worse median OS in those with anti-Yo (13 months) and anti-Hu (7 months) antibodies compared to those with anti-Tr (>113 months) and anti-Ri (>69 months) antibodies [80]. In another series following patients with breast or gynecologic cancer and PCD over a median of 84 months or until death, median OS was 22 months in those with gynecologic cancers compared to 100 months in the breast cancer group [85]. Similarly, Hammack et al. [86] observed that patients with positive anti-Yo antibody survived for only 17.3 months compared to 39.9 months in those with negative antibody titers.

Given that many patients are treated with multiple agents simultaneously and the rarity of PCD, it has proven difficult to systematically study the efficacy of individual treatment modalities [81]. The general consensus is that early diagnosis of PCD is critical as unrecognized and untreated disease inevitably leads to irreversible loss of Purkinje cells. As with all PNS, treatment of PCD is based on primary tumor control and removal of circulating antibodies with immunosuppressive or -modulatory therapy with the goal to reduce antigenic burden. With ovarian cancers, this encompasses surgical resection, maximal cytoreduction, and platinum-based chemotherapy [88]. Corticosteroids are typically given as IV methylprednisolone (1 g daily) for 3–5 days, followed by oral prednisone (60–80 mg daily). An alternative regimen is repeated courses of high-dose methylprednisolone [81].

The benefit of IVIG in anti-Yo antibody-associated PCD is controversial [81]. A typical dose is 2 g/kg over five days and 1–2 g/kg for repeated courses [81]. No improvement was seen in four patients with PCD and anti-Yo antibodies treated with one to 11 courses of IVIG [90]. A combined approach of IVIG, cyclophosphamide (600 mg/m^2 at day 1), and methylprednisolone (1 g daily from day 1 to 3) was also disappointing; it stabilized disease in one-third of patients with a modified Rankin scale (mRS) ≤ 3 (ambulatory) for up to 35 months but had no impact on disease progression in those with mRS $\geq$ 4 (bedridden) [91].

PCD is thought to be mediated by cellular rather than humoral immunity as supported by recent treatment results with T and B cell-targeting agents. In one trial, patients received combined tacrolimus (0.15–0.3 mg/kg daily in two divided doses) and prednisone (60 mg daily, followed by a taper over one to four weeks) [92]. Tacrolimus is a T cell inhibitor with good BBB penetration and steroids may induce apoptosis in mature T cells [93], resulting in potent induction of T cell death [92]. Thirteen patients with anti-Yo antibody and ovarian cancer were included, and significant subjective neurologic improvement was observed in eight of them. Median OS was 38 months, which is longer than in other studies [85]. In addition, there was a significant lowering of median CSF WBC count, thus substantiating the role of cellular immunity in the pathogenesis of PCD.

By contrast, rituximab (RTX) , a monoclonal antibody against CD20 used to treat B cell malignancies, has not shown convincing benefit. In a case series of nine patients (eight with anti-Hu and one with anti-Yo antibody), only one-third improved by ≥ 1 point on mRS (two with anti-Hu and one with anti-Yo antibody) [94]. The lack of improvement with RTX may support the predominant role of T cells in disease pathogenesis.

Plasma exchange (PLEX) has demonstrated variable efficacy [81]. Some studies did not show any objective improvement with PLEX [86], while others did in 50% of patients when PLEX was given with cyclophosphamide or cancer-directed treatment [95]. The trend was less favorable for those with gynecologic cancers and anti-Yo antibodies (27% with improvement) than those with other onconeural antibodies (71% with improvement) [95], again highlighting the more dismal prognosis associated with anti-Yo antibodies.

Anti-NMDA Receptor Encephalitis

Anti-NMDAR encephalitis is the most common autoimmune encephalitis after acute demyelinating encephalomyelitis [96] and, in young individuals, occurs much more frequently than any type of viral encephalitis [97]. It is thought to be the most common cause of paraneoplastic encephalitis [98].

The key mediators of anti-NMDAR encephalitis are IgG antibodies against the NR1 subunit of N-methyl D-aspartate (NMDA) receptors, which are prominently distributed on the cell membranes of GABAergic neurons [99, 100], resulting in various downstream effects, including disinhibition of excitatory pathways and concurrent release of glutamate in the extracellular space [98]. It also affects dopaminergic, noradrenergic, and cholinergic pathways, which may explain the prominent autonomic instability seen in this disease. Involvement of the brainstem respiratory center leads to central hypoventilation [98].

The typical patient is a young woman who presents with prominent psychiatric symptoms, including behavioral disturbance, psychosis, grandiose delusions, catatonia, anxiety, and paranoia [98, 101]. A history of a viral-like prodrome predating the onset of psychiatric features by a few days to two weeks may be elicited in up to 70% of patients [98]. Significant language difficulties, ranging from decreased speech output and echolalia to mutism, are often seen [98]. The psychiatric features then progress to development of memory loss and decreased level of consciousness. Movement abnormalities, including orofacial dyskinesias, choreoathetosis, dystonia, rigidity, and oculogyric crisis are common, as is autonomic dysfunction, which typically presents with hyperthermia, fluctuating blood pressure and heart rate, hypersalivation, and genitourinary dysfunction [98]. Central hypoventilation, along with impaired level of consciousness and status epilepticus, often necessitates intubation and prolonged ventilator support [98, 101]. Seizures occur early and invariably and often progress into status epilepticus [98].

The above clinical constellation, especially in a young woman, should prompt an immediate work-up for anti-NMDAR encephalitis and thorough search for an underlying malignancy as timely implementation of treatment hastens recovery and improves prognosis [101]. The associated tumor is almost always an ovarian teratoma, which expresses NMDAR [102, 103]. In some cases, no underlying tumor is found despite extensive screening; this is more common in younger (age < 12) and nonblack patients [98, 101]. Diagnostic evaluation should include CT or MRI of the chest, abdomen, and pelvis, pelvic and/or transvaginal ultrasound, contrast-enhanced brain MRI, CSF studies, and testing for paraneoplastic antibodies.

CSF studies typically show a lymphocytic pleocytosis and normal or mildly elevated protein levels. CSF oligoclonal bands are found in 60% of afflicted individuals [98]. The presence of NMDAR antibodies in CSF or serum confirms the diagnosis. CSF NMDAR antibody is more sensitive than serum NMDAR antibody (100% versus 85.6%), and higher CSF titers have been observed in those with clinical relapses, underlying teratoma, and poor outcome (defined as mRS $\geq$ 3). Specificity is 100% for both CSF and serum NMDAR antibodies [104].

Brain MRI and EEG are useful to exclude other causes of encephalitis and altered mental status but lack sensitivity and specificity. MRI can be normal in up to half of patients [105]. Alternatively, it may show T2/FLAIR hyperintensity in the hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, and basal ganglia, with or without associated enhancement in these areas or the meninges [98]. Brain atrophy can occur as a result of intractable seizures. EEG frequently shows nonspecific slowing, epileptiform discharges, and electrographic seizures [98].

In addition to removal of the underlying tumor, first-line treatment includes corticosteroids plus IVIG or PLEX [98]. Second-line therapy is added if patients experience little to no improvement with first-line treatment. This typically consists of combined RTX (375 mg/m^2 every week for four weeks) and cyclophosphamide (750 mg/m^2 with first dose of rituximab, then monthly thereafter) [98, 101]. Most physicians treat until a satisfactory clinical response has been achieved.

Overall prognosis is good but clinical recovery can take months to more than a year. In an observational study of 577 patients, 81% of patients had a significant clinical response to tumor removal and first-line immunotherapy at a median follow-up time of 24 months [101]. Recovery continued to occur until 18 months of follow-up. Prompt initiation of

immunotherapy, tumor removal, and lower symptom severity were independent predictors of a favorable outcome [101]. In addition, patients with an underlying ovarian teratoma tend to perform better neurologically than those without [98]. In those failing first-line immunotherapy, the addition of second-line therapy led to improved clinical outcome, compared to those who did not receive second-line therapy [101]. Relapses occur more frequently in those without an underlying tumor and who do not receive immunotherapy [101]. Mortality in anti-NMDAR encephalitis is 4–7% [101, 106], and patients typically succumb to medical complications, neurologic deterioration, or tumor progression.

Paraneoplastic Peripheral Neuropathies

Paraneoplastic peripheral neuropathies (PNs) are one of the more common paraneoplastic manifestations of cancer and typically seen in SCLC, thymoma, and hematologic disease (monoclonal gammopathy of undetermined significance (MGUS), Waldenström's macroglobulinemia, and lymphoma) [107]. Their incidence in gynecologic cancers is low. They have been reported in cancer of the ovary, endometrium, and cervix [76, 108–110]. The neuropathy is usually axonal and either sensory-predominant [76], motor-predominant [108], or mixed sensorimotor [109, 110]. Concurrent involvement of the dorsal root ganglia (neuronopathy) is possible [76]. Whereas paraneoplastic PNs observed in SCLC and thymoma often associate with a specific onconeural antibody (such as anti-Hu or anti-CRMP antibody) [111], such an association is less clear for PNs in gynecologic cancers. For instance, in a series of patients with gynecologic malignancies and paraneoplastic PN, two were positive for anti-Hu antibody, one had atypical antibody, and two were negative for onconeural antibodies [76]. No clear data on response to treatment and prognosis exist. In the aforementioned case series [76], one patient with cervical cancer had progressive disease despite treatment with steroids whereas another with ovarian cancer improved with IVIG. Another case had improvement of neurologic symptoms after resection of an endometrial carcinoma [108].

Opsoclonus Mycolonus Syndrome

Opsoclonus myoclonus syndrome (OMS) is typically a disease of childhood and associated with neuroblastoma [112]. Adult-onset disease is much rarer and usually develops over a course of a few weeks. Patients present with truncal ataxia, gait problems, falls, and myoclonus. The myoclonus can affect different body segments (limbs, truncal, craniocervical) and cause dysarthria and dysphagia [113]. Opsoclonus refers to involuntary, chaotic, multidirectional, and irregular saccades, causing vision abnormalities. Patients can be afflicted by other symptoms secondary to brainstem and cerebellar involvement and present with encephalopathy [113].

OMS can be paraneoplastic, parainfectious, toxic/metabolic, autoimmune, or idiopathic in origin [113]. An underlying tumor is rarely found; if present, it is most commonly SCLC or breast cancer [113, 114]. An association with gynecologic cancers is even less common but has been reported in patients with ovarian and fallopian tube carcinoma [76, 113–115] and ovarian teratoma [116]. In a case series of 92 patients with breast or gynecologic malignancy and definitive or possible PNS, four had OMS (three breast and one ovarian carcinoma) and two had positive anti-Ri antibody [76]. A paraneoplastic antibody is only found occasionally, most commonly anti-Ri antibody [113, 117]. Brain MRI is often normal but can show T2/FLAIR hyperintensity in the dorsal pons or midbrain [118].

Based on uncontrolled observational studies, response to treatment is good. Klaas and coworkers reviewed 21 patients with OMS and found that most achieved clinical remission with immunotherapy (corticosteroids and/or IVIG) and symptomatic therapy (benzodiazepines, levetiracetam, valproic acid, and gabapentin) and remained symptom-free upon discontinuation of therapy [113]. Long-term immunosuppression, e.g., with mycophenolate mofetil, was rarely needed [113]. Prognosis is better for those without an underlying cancer and, if present, for those who undergo targeted treatment of their neoplasm [117]. A suggested treatment plan is a short course of IV methylprednisolone or IVIG for 3–5 days, followed by weekly infusions for six weeks. Patients refractory to this regimen may be considered for combination immunotherapy and PLEX [113]. Lastly, rare cases of complete response to clonazepam (8–12 mg) and topiramate have been reported [119, 120].

Hypercoagulability and Non-bacterial Thrombotic Endocarditis

Hypercoagulability of malignancy is mediated by a number of factors, including increased pro-coagulant activity and decreased fibrinolytic activity [121]. Non-bacterial thrombotic endocarditis (NBTE) is a rare manifestation of cancer-related hypercoagulability that has been described in association with gynecologic tumors, most commonly ovarian cancer, although cases of endometrial cancer have also been reported [122, 123]. Arterial thromboembolic complications include arterial strokes in multiple vascular territories and myocardial infarctions. Venous embolic

events can manifest as deep venous thromboses in the lower extremities and pulmonary emboli [122]. Transthoracic or -esophageal echocardiogram reveals vegetations, typically on the mitral or aortic valve. Blood cultures are characteristically negative. The underlying gynecologic tumor can be benign [123] or malignant and of various histologic grades and stages [122, 124, 125]. Notably, NBTE has been observed more frequently in adenocarcinomas than other histologic subtypes [126]. Treatment of NBTE involves treatment of the underlying cancer and anti-coagulation, preferably low-molecular weight heparin [127].

Treatment-Related Complications of Gynecologic Cancers

Surgery-Induced Peripheral Nerve Injuries

The incidence of peripheral nerve injury after gynecologic surgery is <2%, based on prospective and retrospective data [128–130]. Injuries can occur through compression, stretch, entrapment, or transection of nerves. The risk of postoperative neuropathy and the distribution of nerve involvement depends on the type of surgery, patient positioning, and duration of surgery. For instance, the lithotomy position carries a higher risk of sciatic, femoral, and peroneal nerve injury. Deep abdominal surgery, including abdominal hysterectomy, is a common cause of femoral neuropathy due to stretch injury from hyperflexion of the thigh and compression of the femoral nerve against the pelvic wall [131]. The risk of compression injury is particularly high with self-retaining retractors [131]. The ilioinguinal and iliohypogastric nerves can be injured with transverse (e.g., Pfannenstiel) incisions, due to entrapment from sutures or neuroma formation during the healing or scarring process [132]. Other potentially affected nerves are the lateral femoral cutaneous, genitofemoral, obturator, and pudendal nerves. Bilateral nerve injury has been reported in as many as 27% of patients [128]. Patients commonly complain of sensory loss or weakness in the distribution of the affected nerve. Pain is less common but can occur with transection or ligation injuries and neuroma formation. Preventive intra-operative measures include appropriate patient positioning (avoiding excessive extension, flexion, abduction, and external rotation) [133], avoiding the lithotomy position for >2 h [134], attention to incisional technique, and positioning of retractor blades.

Treatment is typically conservative and, in most cases, symptoms resolve over weeks to months. In one study, all but one patient (91%) had complete resolution of neuropathic symptoms after a median of 31.5 days (range of 1 day–6 months) [128].

Radiation-Induced Lumbosacral Plexopathy

Patients with gynecologic cancers may receive pelvic XRT or brachytherapy, which can damage regional nerves via direct toxicity on axons, myelin, and the vasa vasorum, with resultant nerve infarction [135]. Radiation-induced lumbosacral plexopathy is a rare but potentially debilitating complication of gynecologic malignancies. It has been reported in cervical, uterine, and ovarian cancer [70, 136, 137]. Onset is typically insidious and can occur months to years after completion of treatment [138]. Toxicity of radiation is dose-dependent but has also been reported at lower doses (1700 cGy) [138]. Vaginal brachytherapy is used in the treatment of locally advanced cervical and uterine cancer to achieve better local disease control and prevent vaginal recurrence [139, 140]. Since most patients receive combined external beam radiation and brachytherapy, it is unclear whether brachytherapy alone significantly increases the risk of regional nerve damage. In a case series of 2410 patients, four cases who had received whole-pelvis XRT and intracavitary brachytherapy for cervical carcinoma developed flaccid lower extremity weakness 8–26 months after completion of radiation [136]. Pain was uncommon.

Careful differentiation of radiation-induced plexopathy from neoplastic plexopathy is important, given the different implications for treatment and prognosis. Radiation-induced plexopathy typically presents with paresthesias, flaccid weakness, and accompanying limb edema. Pain, the hallmark of neoplastic plexopathy (present in 98% of patients), is less prominent (10%) in radiation-induced injury [138]. Electromyogram (EMG) may reveal myokymia, which is generally absent in neoplastic or compressive plexopathy [138]. The imaging modality of choice is contrast-enhanced MRI of the plexus. With tumor- but not radiation-related injury, enhancement of the nerve roots is common, although radiation can produce T2-weighted hyperintense changes [141]. Most importantly, the absence of local tumor on imaging suggests a treatment-related rather than neoplastic etiology.

Management of radiation-induced plexopathy is primarily symptomatic and focuses on pain control, physical therapy, and rehabilitation. Although frequently used, there is no evidence that hyperbaric oxygen is beneficial [142, 143]. Unfortunately, most patients experience progressive functional decline [138].

Chemotherapy-Induced Peripheral Neuropathy

Platinum-based agents and taxanes are frequently used in the treatment of gynecologic cancers but are notoriously known

to cause peripheral neuropathy. Cisplatin causes an axonal neuropathy of primarily large myelinated sensory fibers in up to 60% of patients receiving a cumulative dose of 225–500 mg/m^2 [144]. The most susceptible site is the dorsal root ganglion. Neuropathic symptoms can persist or worsen even after discontinuation of the drug [145]. The risk of peripheral neuropathy with carboplatin at conventional doses is lower than with cisplatin [144]. Paclitaxel and docetaxel can also cause a predominant sensory neuropathy. Paclitaxel appears to be more neurotoxic than doxetaxel, with an incidence of approximately 60 and 15%, respectively [146, 147]. As for platinum-based agents, the cumulative dose is the main risk factor for taxane-induced peripheral neuropathy, with a neurotoxic threshold of 1000 mg/m^2 for paclitaxel and 400 mg/m^2 for docetaxel [148].

In addition, cisplatin has been associated with dose-dependent ototoxicity, which typically manifests with bilateral and irreversible sensorineural hearing loss, ear pain, and tinnitus [149]. The underlying mechanism involves deposition of the drug and generation of reactive oxygen species in the cochlea, outer hair cells, spiral ganglia, stria vascularis, and spiral ligament. There is insufficient evidence to support use of any particular agent (such as vitamin E, sodium thiosulfate, or amifostine) to prevent cisplatin-induced ototoxicity [149].

Conclusions

Gynecologic cancers can cause a variety of neurologic complications via direct malignant cell infiltration of the nervous system, paraneoplastic phenomena, and treatment-related effects. CNS metastases from gynecologic tumors are rare except with choriocarcinoma and generally portend an unfavorable prognosis. Paraneoplastic cerebellar degeneration and anti-NMDAR encephalitis are well-characterized paraneoplastic syndromes associated with ovarian tumors and should be considered in any woman presenting with typical symptoms. Lastly, with the development of more sophisticated treatment modalities and improved survival in patients with gynecologic cancers, the incidence of long-term surgery-, chemotherapy-, and radiation-related neurologic complications will likely increase.

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