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Gynecological Malignancy

Paraneoplastic Syndromes Associated with Gynecologic Neoplasms: Experience from a Tertiary Care Center in South India

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Abstract

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Paraneoplastic syndromes associated with gynecologic neoplasms are rare and can involve various organ systems including the central nervous system, hematopoietic system, musculoskeletal, dermal and endocrine systems. They can result from cancer-associated immune reactions or the production of ectopic substances by the tumor tissue. This study retrospectively reviews the clinical presentations, management and outcome of patients who presented with paraneoplastic syndromes associated with gynecologic malignancies. Retrospective data were collected from medical records of patients who exhibited paraneoplastic symptoms associated with gynecologic neoplasms and were managed by department of gynecologic oncology at a tertiary care hospital in South India between 2014 and 2021. Medical case records of all eligible patients were reviewed, identifying eight women with gynecological neoplasms who presented with associated paraneoplastic symptoms. Among them, two cases pesented with paraneoplastic neurologic syndromes, four cases with paraneoplastic dermatologic syndromes, including three cases of dermatomyositis and one case with multicentric reticulohistiocytosis, and two cases with hypercalcemia. Paraneoplastic syndromes are rare manifestations that can precede or develop following the diagnosis of a malignancy. They require integrated management by a multidisciplinary team including physicians and oncologists. Early recognition of these symptoms and prompt evaluation have the potential to improve the prognosis and quality of life, at least in a small fraction of patients.

Keywords

- paraneoplastic syndrome
- paraneoplastic cerebellar degeneration
- dermatomyositis
- ovarian cancer
- multicentric reticulohistiocytosis
- paraneoplastic hypercalcemia

Introduction

Paraneoplastic syndromes are clinical manifestations associated with malignancies that cannot be attributed to direct tumor growth, metastasis, or treatment-related side effects. They were first described to explain the symptoms of multiple cranial and radicular neuropathies in a patient with uterine neoplasm.[1] It results from either hormones, cytokines, and other substances produced by the tumor or due to the host antitumor immune response. In gynecologic practice, paraneoplastic syndromes have been reported in association with both benign and malignant conditions. Lack of

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data and awareness regarding paraneoplastic manifestations can often delay the diagnosis of underlying malignancy and adversely affect the morbidity, quality of life, and prognosis of cancer patients.

This article summarizes eight cases of gynecologic neoplasms that presented with various paraneoplastic syndromes.

Materials and Methods

Medical records of patients who presented with paraneoplastic symptoms associated with gynecologic neoplasms in the department of gynecologic oncology at a tertiary care center in South India over a period of 8 years (January 2014–December 2021) were reviewed. The details of clinical presentation, investigations, and treatment were accessed.

Results

Paraneoplastic Neurological Disease

Autoimmune Demyelinating Polyneuropathy with Anti-Yo Antibody Positive Paraneoplastic Cerebellar Degeneration

A 50-year-old postmenopausal woman presented with light headedness followed by gradual onset motor weakness involving all four limbs and difficulty in swallowing. After admission to the hospital, she developed signs of impending respiratory failure and was shifted to intensive care unit. On examination, Eastern Cooperative Oncology Group (ECOG) performance score was 4, and bilateral inguinal lymph nodes were palpable (4 cms in size).[2] Central nervous system examination revealed vertical and gaze evoked nystagmus with mild horizontal gaze restriction. Muscle tone was reduced in all four limbs with absent deep tendon reflexes. There was no sensory deficit. Abdomen examination revealed watery discharge from umbilicus and a vague suprapubic mass on palpation.

Magnetic resonance imaging (MRI) brain and spine were normal. Cerebrospinal fluid (CSF) analysis revealed albumino-cytological dissociation. Electroneur omyography showed impersistent F waves in bilateral lower limbs. With a provisional diagnosis of autoimmune demyelinating polyneuropathy (AIDP), the patient was started on intravenous immunoglobulin (IVIg) followed by methylprednisolone and rituximab. A contrast-enhanced computed tomography (CECT) of abdomen and pelvis revealed the presence of a heterogeneously enhancing lesion involving the right adnexa measuring $6.5 \times 5.6 \times 6.1$cm with extension into mesentery and invasion of adjacent pelvic organs. There were multiple deposits in liver, omentum, mesentery, and lymph nodes (pelvic and inguinal nodes). The largest abdominal lesion measured $6.5 \times 7.3 \times 6.1$cm (liver parenchyma) infiltrating the pylorus of the stomach (►Fig. 1A and B). Serum CA-125 was elevated (11,970 U/mL), Carcinoembryonic antigen (CEA) was normal (CA125: CEA ratio more than 25). In view of neurological symptoms and suspected malignancy, a paraneoplastic neuronal antibody panel was done, which showed strong positivity for anti-Yo antibody. Biopsy from the left inguinal lymph node was suggestive of metastatic high grade serous carcinoma with WT1 (2 + 90%), and CK7 (2 to 3+ >90%) positive with mutated p53 (3 + 90%). A diagnosis of high grade serous ovarian carcinoma-International Federation of Gynecology and Obstetrics (FIGO) stage IVB with associated paraneoplastic neurological disease (PND) was made.[3] In view of poor performance status, comorbidities and high disease burden, the patient received neoadjuvant chemotherapy with intravenous paclitaxel and carboplatin.

Response assessment was done after four cycles of chemotherapy. The inguinal lymph nodes were palpable without any reduction in size, CA 125 was 1,726 IU/mL. Repeat CECT showed tumor persisting in the right adnexa and left lobe of liver (largest dimension—3.7 cms). The patient's relatives were counseled regarding the disease status and given the option of interval debulking surgery (with less likelihood of achieving R0 resection) versus continuation of chemotherapy.

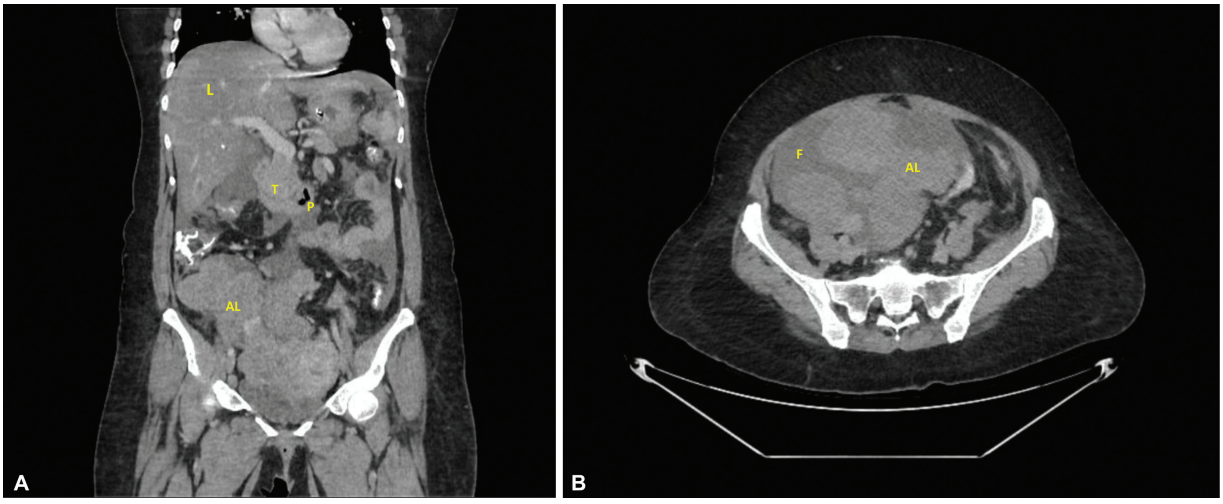

Fig. 1 (A) Contrast-enhanced computed tomographic (CT) image of abdomen and pelvis (coronal view) showing heterogeneously enhancing soft tissue lesion in right adnexa extending into the mesentery (AL); T, tumor depicting loss of fat planes with the pylorus of the stomach (P); L, liver. (B) Contrast-enhanced CT image of pelvis (axial view) showing heterogeneously enhancing right adnexal lesion (AL) with free fluid in the pelvis (F).

They opted for continuation of chemotherapy. She received a total of six cycles of platinum-based intravenous chemotherapy. Presently, her tumor burden is stable. However, she has developed muscle wasting and contractures without significant improvement in neurological symptoms.

Anti-NMDA Receptor Encephalitis

A 23-year-old female presented with complaints of poor performance in studies and depression for the last 2 months followed by development of irritability and hallucinations for 10 days. Brain MRI was normal. In view of suspected paraneoplastic syndrome, antineuronal antibody testing was done that showed positive anti-NMDA(N-methyl-D-aspartate) receptor antibodies. Transabdominal ultrasound examination revealed a complex right adnexal mass measuring 6×5cm with calcification, fat components, and acoustic shadowing, suggestive of mature cystic teratoma. Patient was scheduled for ovarian cystectomy but opted for surgery elsewhere due to financial constraints.

Paraneoplastic Dermatologic Syndromes

There were a total of four cases of ovarian/peritoneal malignancies that presented with paraneoplastic dermatologic manifestation (three cases of paraneoplastic dermatomyositis and one case of multicentric reticulohistiocytosis [MRH]) (►Table 1). In all the four cases, the tumor was detected at an advanced stage that is often the scenario with malignant neoplasms of the ovary. The clinical details and management are discussed in ►Tables 1 and 2, respectively.

Hypercalcemia

There were two cases of paraneoplastic hypercalcemia associated with malignancy.

Case 1: A 60-year-old female presented with abdominal distension, altered sensorium, tremors, and myalgia. Laboratory tests revealed total serum calcium—14.0 mg/dL, phosphate—2.1mg/dL, and parathyroid hormone—7.0pg/mL. Abdominal ultrasound revealed a solid cystic lesion arising from uterine fundus with multiple omental deposits. Biopsy from the abdominal mass was suggestive of malignant spindle cell neoplasm favoring leiomyosarcoma. As the performance status of the patient was poor, she was planned for neoadjuvant chemotherapy. Hypercalcemia was managed with hydration, loop diuretics, and injection zoledronate. However, due to poor prognosis relatives opted for discharge against medical advice. She expired a month later.

Table 1 Clinical details of cases with paraneoplastic dermatologic syndromes

Case no.	Age (in years)	Presenting symptoms/signs	Relevant investigations
1	59	Case of triple negative breast cancer treated with surgery and radiotherapy in 2017 • Complaints of skin rash 3 years after completing treatment-diagnosed with amyopathic dermatomyositis and started on immunotherapy; initial workup for malignancy was negative • Incidentally diagnosed with a complex adnexal mass 1 year after the diagnosis of dermatomyositis	• Anti-TIF 1-γ positive • CPK-307 U/L • CA 125–121.9 U/mL • PET-CT-enhancing mass lesion in right adnexa
2	35	• Proximal muscle weakness • Skin rash	• CA-125–145.3 U/mL • CPK-1434 U/L, LDH-497U/L • EMG-bilateral median motor and sensory axonal neuropathy and bilateral common peroneal motor axonal neuropathy • Contrast-enhanced CT scan-bilateral solid cystic adnexal masses measuring $3.6 \times 8.7 \times 3.8$ cm on the right side and $3.4 \times 5.8 \times 3.7$cm on the left side. Few enlarged pelvic lymph nodes noted
3	66	• Skin rash • Abdominal distension	• CA 125–259.5 U/mL • Creatinine phosphokinase- 42 U/L • Skin biopsy-dermatomyositis • PET-CT-ascites with nodular peritoneal thickening
4	57	• Nodular lesion in the scalp and pinna (►Fig. 2)	• Scalp biopsy-histiocytic proliferation with predominance of xanthomatized histiocytes • CECT abdomen and pelvis-enhancing soft tissue lesion in left adnexa with multiple soft tissue deposits in abdomen and omentum • CA 125–374U/L

Abbreviations: CECT, contrast-enhanced computed tomography; CPK, creatinine phosphokinase; EMG, electromyography; LDH, lactate dehydrogenase; PET-CT, positron emission tomography-computed tomography; TIF-γ, transcriptional intermediary factor-gamma

Table 2 Treatment details of cases with paraneoplastic dermatologic syndromes

Case no.	Primary gynecologic neoplasm	Associated paraneoplastic syndrome	Treatment	Present status
1	High-grade serous primary peritoneal carcinoma stage IIIA1(i)	Amyopathic dermatomyositis	• Immunotherapy • Primary debulking surgery with six cycles of platinum-based adjuvant chemotherapy	• Platinum-resistant disease diagnosed at 3 months follow-up • On cyclophosphamide metronomic therapy • Overall survival (OS) 12 months
2	High-grade serous carcinoma ovary IIIA2	Dermatomyositis	• Immunotherapy • Primary debulking surgery with six cycles of platinum-based adjuvant chemotherapy	• Diagnosed with partial platinum sensitive recurrence at 11 months • Started on palliative chemotherapy • Expired 1 month after diagnosis of recurrence • OS 12 months
3	Primary peritoneal carcinoma stage IIIC	Dermatomyositis	• Immunotherapy • Platinum neoadjuvant chemotherapy followed by interval debulking surgery and platinum-based adjuvant treatment	• Currently under regular follow-up and disease free till date • Disease-free survival (DFS)—6 years
4	High-grade serous carcinoma stage IIIC	Multicentric Reticulohistiocytosis	• Steroids and methotrexate • Primary debulking surgery followed by six cycles of adjuvant platinum-based chemotherapy	• Skin lesions resolved after treatment • Currently under follow-up and disease free till date` • DFS—2 years

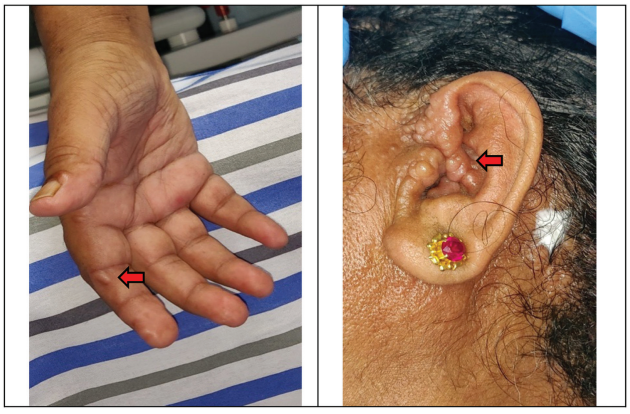

Fig. 2 Papulonodular lesions of multicentric reticulohistiocytosis involving digits and pinna (red arrow)

Case 2: A 52-year-old lady with carcinoma vulva who was advised upfront chemoradiation in view of FIGO stage IVA disease presented with severe myalgia.[4] On examination, ECOG performance score was 4 and there was a proliferative growth approximately 5×6cm involving right labia with necrotic left inguinal lymph node approximately 7×8cm^2. Laboratory investigations revealed hypercalcemia with serum total calcium—11.3mg/dL, phosphorous—3.94mg/dL, magnesium—2.4mg/dL, plasma vitamin D—3.5ng/mL, and parathyroid hormone—2.4pg/mL. Hypercalcemia was managed with hydration, loop diuretics, and injection zoledronate. Palliative measures were initiated as opted by the patient and she was discharged at request for home-based care. She expired 1 month later.

Discussion

Paraneoplastic syndrome can precede the diagnosis of tumor or can develop following the treatment initiation. The incidence of paraneoplastic syndromes in gynecological cancers is grossly underestimated owing to the lack of awareness and diagnostic difficulties linked to the condition.

Majority of paraneoplastic disorders of the CNS are immune mediated. The specific diagnostic criteria along with detection of onconeural antibodies help in diagnosis of this condition.[5] Commonly diagnosed PND include paraneoplastic cerebellar degeneration (PCD) and paraneoplastic encephalitis.

Paraneoplastic cerebellar degeneration often has a rapid onset and progression resulting from destruction of Purkinje cells in the cerebellum. Since the process is irreversible, the prognosis in PCD remains grave.[6] Various antibodies are reported in association with PCD, with the commonest being anti-Yo antibody as observed in our case.[7] It is often reported with malignancies of breast, ovary, and other gynecological cancers.

Guillain Barré syndrome (GBS) is an AIDP resulting from humoral and cell-mediated immune responses directed against peripheral nerves. It often occurs after respiratory/gastrointestinal infections or immunizations. Although rare, there are few case reports and a cohort study that have documented the association of paraneoplastic GBS with ovarian carcinoma.[8–10]

Based on the history, clinical findings, and laboratory values, our patient was diagnosed with features of paraneoplastic AIDP with cerebellar degeneration.

There are no guidelines recommending a standard treatment protocol for PND due to paucity of cases. Early initiation of antitumor therapy offers the greatest chance for PND stabilization.[11] Corticosteroids, plasma exchange, and IVIg have failed to demonstrate significant benefit in anti-Yo positive PCD.[12–14] One of the above studies have reported improvement in neurological Rankin Scale score after four cycles of rituximab in PCD with ovarian cancer.[14] In the present case, upfront surgery was not feasible due to extensive disease burden and poor performance status of the patient. Immunotherapy and rituximab did not demonstrate any significant improvement in her neurological symptoms.

Neurological outcome and survival in patients with PCD vary significantly with the type of onconeural antibodies. In a study conducted by Shams'ili et al, the median survival in patients with a positive anti-Yo antibody was 13 months from the time of diagnosis.[14]Patients receiving antitumor treatment (with or without immunosuppressive therapy) had longer survival.

Encephalitis related to paraneoplastic syndromes can be classified according to the antibodies associated with them, for example, anti-Hu related to small cell carcinoma of lung, anti-Ma2 associated with testicular germ cell tumor, and anti-NMDA receptor antibody commonly associated with ovarian teratomas.

NMDA receptors are glutamate gated ion channels, widely expressed in CNS. In anti-NMDA receptor encephalitis, the neural elements in mature teratoma express ectopic NMDA receptors, stimulating production of antibodies that cross react with receptors in CNS resulting in neurologic and psychiatric symptoms.[15] The diagnostic criteria comprise abnormal behavior, speech dysfunction, seizures, movement disorders, decreased level of consciousness, autonomic dysfunction, or central hypoventilation. Presence of any three of the enlisted symptoms along with ovarian teratoma is sufficient to establish a provisional diagnosis of paraneoplastic anti-NMDA receptor encephalitis. Our patient had presented with behavioral disturbances including, depression, hallucination, and irritability. Definite diagnosis is made upon the detection of anti-NMDA receptor antibodies in blood or CSF.

Thiyagarajan et al described four cases with autoimmune encephalitis associated with ovarian teratoma, who presented with neuropsychiatric manifestations. One out of four patients had a seronegative autoimmune encephalitis but was diagnosed with an ovarian teratoma on laparoscopic right salpingo-oophorectomy. Patient showed improvement in neuropsychiatric symptoms after surgery. The remaining three patients were diagnosed with positive anti-NMDA receptor antibody in CSF.[16]

Treatment involves a combination of early resection of tumor and immunotherapy (IVIg, steroids, rituximab, and plasma exchange). It is reported to provide improvement in neurological outcome in 81% of cases.[17]

Dermatomyositis is an autoimmune myopathy associated with cutaneous manifestations and has paraneoplastic association in about 25% of cases.[18] Paraneoplastic dermatomyositis are commonly described in association with ovarian and bladder malignancies. Risk of ovarian malignancies is increased five- to ten-folds in patients with dermatomyositis.[7] The classic presentation includes characteristic skin rash in sun-exposed areas and symmetrical proximal muscle weakness. Symptoms often precede the diagnosis of ovarian cancer as observed in our cases. Serum creatinine kinase levels can indirectly reflect the extent of muscle damage. Diagnosis of adult dermatomyositis must prompt physicians to investigate further for the presence of an underlying malignancy. In case 1 in our series, the peritoneal malignancy was detected a year after starting treatment for amyopathic dermatomyositis. This emphasizes the importance of surveillance in patients with dermatomyositis whose initial malignancy workup is negative. Steroids and immunosuppressive therapy have shown benefit in relieving the symptoms in patients with paraneoplastic dermatomyositis.

In a study by Cheng et al, a propensity score matching of 23 patients with concurrent ovarian cancer and dermatomyositis and 115 patients with ovarian cancer without dermatomyositis was reported. The 5-year overall survival rates and progression-free survival rates were poorer for the dermatomyositis group. They concluded that a correlation and parallel clinical course exists between the two diseases.[19]

MRH is a rare entity that classically presents with small reddish-brown nodules and papules distributed over face, hands, ears, and multiple joints. Our patient also presented with scalp nodules and bilateral knee joint pain. In 25% cases, it is associated with an underlying malignancy suggesting paraneoplastic etiology. Malignancies of breast, ovary, endometrium, and cervix are commonly reported with MRH. Stimulation of histiocytes by cytokines results in immune-mediated rheumatologic and cutaneous manifestations. It is characterized by tissue infiltration and proliferation of histiocytes and multinucleated giant cells that result in the release of cytokines. The stimulus for the histiocyte infiltration is not fully understood.[20]

Kishikawa et al reported a case of ovarian cancer with multicentric histiocytosis. The patient presented with skin lesions and joint pain and was started on steroid and methotrexate. Two months following the diagnosis of multicentric histiocytosis, she developed abdominal distension and was diagnosed with poorly differentiated serous ovarian cancer. She underwent surgery followed by systemic chemotherapy. They reported a complete resolution of her skin and joint symptoms at the completion of treatment for malignancy.[21]

Treatment of malignancy often results in regression of symptoms of MRH. Our patient also had a complete

resolution of skin and joint symptoms at the completion of treatment.

Paraneoplastic hypercalcemia results from parathyroid hormone-related peptide (PTHrP) released by malignant cells and is referred to as humoral hypercalcemia of malignancy. Various gynecological malignancies are associated with it, most common being small cell and clear cell carcinomas of ovary.[22] The commonest clinical manifestations include bone pain, renal failure, abdominal discomfort, and behavioral changes resulting from CNS affection. Laboratory values demonstrate an increased serum calcium, with normal or low PTH and increased PTHrP levels. The patients are often dehydrated due to increased renal water loss resulting from nephrogenic diabetes insipidus. Most important step in acute management is adequate hydration after ruling out renal compromise, followed by the use of bisphosphonates to reduce serum calcium levels. Majority of paraneoplastic hypercalcemic syndromes are observed in association with disseminated disease and hence are indicative of poor prognosis, as observed in two of our cases. The removal of primary tumor plays an important role in the management of paraneoplastic hypercalcemia. Şükür et al reported a case of early vulvar carcinoma that presented 4 months after primary surgery with distal recurrence and associated hypercalcemia. The patient expired 5 months after the primary diagnosis due to complications related to hypercalcemia.[23]

Since the onset of symptoms in most cases of paraneoplastic syndromes precedes the detection of malignancy, an attempt should be made for early identification of these symptoms and a search for an underlying malignancy should be conducted. If the presence of the tumor is not identified in initial workup, these cases should be kept under surveillance. Clinicians should be made aware of this entity that can prompt them to manage or refer patients as required. Apart from oncological management, this condition often requires involvement of a multidisciplinary team involving other medical specialists as well. Further studies evaluating the benefit of immunotherapies in those with paraneoplastic syndromes are also warranted that can improve the outcomes, especially in those with paraneoplastic neurologic diseases.

Conflict of Interest

None declared.

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