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An Enigma of Female Psychosis: Case Report and Literature Review of Therapeutic Strategies in Paraneoplastic Encephalitis Associated with Ovarian Teratoma

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Abstract

Introduction: Paraneoplastic Encephalitis (PNE) is the neuropathological disorder of central nervous system, associated with a remote tumor, which presents with diverse of neuropsychological symptoms. There is still a deficiency of an aptly formulated management protocol.

Case report: We report the first case of anti- NMDA-R PNE secondary to ovarian teratoma from Pakistan, in a 17 year old girl that presented with acute psychosis. She underwent immediate tumor excision with plasmapheresis followed by a combination of corticosteroids and IV immunoglobulin therapy. The patient relapsed after a month despite the treatment presenting with mild psychosis, memory loss and cognitive impairment. Provided along with the case report is an extensive literature review (2010-2017) on previously reported cases of PNE with ovarian teratoma to improve understanding of current management of this form of encephalitis.

Conclusion: Paraneoplastic encephalitis is a critical yet reversible illness. Our comprehensive review and experience can be summarized in the following guidelines signifying the current clinical practices regarding PNE with ovarian teratoma. (I) PNE should be suspected in female patients presenting with an acute history of neuropsychiatric symptoms. (II) Tumor resection should be performed earliest to improve patient outcomes.(III) Administration of plasma exchange therapy in immediate postoperative period is recommended. (IV) Pulse therapy preceding intravenous immunoglobin therapy improves patient prognosis. (V) Patients should be discharged on maintenance dose of corticosteroids. (VI) Long term follow up is recommended to monitor for relapses.

Keywords: Ovarian teratoma; Paraneoplastic encephalitis; Acute psychosis

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Introduction

Paraneoplastic encephalitis (PNE) is a multifocal inflammatory disorder of the central nervous system (CNS) associated with remote neoplasia. PNE is known to present with subacute onset of short-term memory loss, episodic seizures, psychiatric manifestations, and neurological or pathologic evidence of involvement of the amygdala and medial aspect of temporal lobes [1]. Antibodies to the N-methyl-d-aspartate subtype of glutamate receptor have been associated with a recently described encephalopathy that has primarily been identified in young females with ovarian tumors. Ovarian teratoma-associated encephalitis was first reported in 1997 [2]. In 2007, an association was identified between this type of encephalitis and N-methyl-D-aspartate receptor (NMDAR) antibodies [3]. NMDAR is a ligand-gated cation channel, comprising NR1 and NR2 subunits, that serves crucial functions in synaptic transmission and plasticity.

The incidence of PNE with ovarian tumors accounts for about 10% of malignancies associated with paraneoplastic syndromes [4]. The international incidence of PEM is by far unknown. Previously reported cases of ovarian teratoma associated with PNE with NMDA antibodies, have shown variable responses to different treatment options that have evolved over the years, based on individual practices. Thus far there are no established guidelines to treat this type of PNE. Previous literature reviews suggest variable recovery outcomes ranging from complete recovery to extensive residual neurologial manifestations, but there has been no report of a relapsing illness in this form of encephalitis. We here report a case of ovarian teratoma associated PNE with NMDA antibodies that presented with a relapse after complete remission. Along with the case report, we also provide an extensive literature review which explains all the current practices and treatment modalities that are being used for anti NMDA encephalitis.

Case Report

A 17 years old female, student by profession, was brought to A & E with presenting complaint of odd behavior since 1 day. According to the informant, she was well and functional until yesterday. The symptoms initiated with irrelevant questioning in the class room and restless at night. She started pacing around in the room, and compliant of inability to sleep. She was unable to recognize the inmates of house and became hostile towards them. Her male cousins also reported acts of disinhibition. There were no crying spells; anhedonia; feeling of hopelessness; feeling of worthlessness; any self-harm behavior or thoughts of grandiosity. There was no history of recent or remote head injury, any recent febrile illness, obsessive thoughts or compulsive behaviors, hallucinations. Substance abuse or exposure to any toxic substance was also denied by the informant. Neither any apparent acute stressor nor trigger was identified. There was no significant past psychiatric history in the patient or immediate family. Patients informant also denied any past episodes of amnesia, unconsciousness, confusion, seizures, and disorientation. On mental state examination, constant self-muttering was present, eyes were closed and she was not following commands. On physical exam, there was hypotonia in all extremities and she was unable to move all her limbs, rest was unremarkable. Her initial investigations showed a hemoglobin level of 8.4 mg/dl and a CRP of 13.97 mg/dl. Urine DR, CSF culture, blood cultures (x3), malarial parasite testing, polymerase assay for tuberculosis, herpes simplex type 1 and 2 antigens, meningococcal, streptococcal, hemophilic, cryptococcal and brucella antigen testing was all negative. Lumbar puncture was in conclusive. Liver function tests and clotting profile was normal. Urine toxicology screen was negative. Serum ceruloplasmin levels were in normal range. Anti dsDNA antibody, ANA antibody, ASMA antibody, AMA antibody and ENA profile were negative. MRI brain was unremarkable. Patients CA-125 levels was raised to 33.50. An ultrasound whole abdomen showed an enlarged heterogeneous mass in the right ovary suggesting evidence of an ovarian teratoma. Patient underwent a laparoscopic surgery for removal of the mass after 15 days of onset of symptoms. Histopathology of the sample showed a mature cystic ovarian teratoma. Patients' blood sample was sent to a Malaysian lab, which showed positive titers for anti NMDA receptor antibodies. Patient was diagnosed anti- NMDA-R encephalitis secondary to ovarian teratoma.

Patient was initially treated with broad spectrum antibiotics along with atypical antipsychotics but did not respond to treatment and her psychosis was persistent. After attaining the above mentioned evidence regarding anti-NMDA antibodies, pulse therapy was administered with intravenous methyl prednisolone 1 g/day for 3 days along with plasma exchange therapy and then was switched to maintenance dose (oral prednisolone 80 mg/day). Patient responded remarkably to treatment. She had complete remission of neurological symptoms. The remission was assessed by progressively increasing scores on BPRS (Basic Psychiatric Rating Scale), MMSE and Modified Ranklein Scale. Patient was discharged with maintenance therapy at home. She was advised to follow up in clinic. Four weeks later, patient came in the clinic with a considerable relapse, in psychosis despite her compliance to steroid therapy at home. She was admitted and intravenous immunoglobulin therapy was initiated along with oral steroid therapy. She had remission with residual cognitive and memory impairment **(Table 1)**.

Discussion

PNE described as, paraneoplastic anti-N-Methyl-D-Aspartate receptor encephalitis association with ovarian teratoma was first documented by Dalmau et al. As per our knowledge, this is the first case to have been reported from Pakistan. In PNE, neurologic dysfunction results from an autoimmune reaction directed against onconeural antigens in the CNS. An over activity of NMDAR may result in toxicity and excitation of the neuron which causes development of neuropsychiatric symptoms in an individual. PNE has been conventionally diagnosed on the basis of the criteria defined by Graus et al., which considers the presence of tumor, antibodies and neurological manifestation [4], as was seen in our patient as well.

According to this current review on PNE with ovarian teratoma reported from 2010-2016, patients suffering from PNE associated with ovarian teratoma presented most commonly with headaches (8 studies), confusion (7 studies) and auditory hallucinations (7 studies), whereas in our patient psychiatric symptoms appeared to be more pronounced in comparison to neurosomatic symptoms as reported in previous studies **(Table 2)**. Gultekin et al., reported short term memory loss as the most common symptom in patients of PNE [3]. Short term memory loss; which is a common presentation in PNE patients was observed in only 4 studies in our review. The presentation of patients with schizophrenia like symptoms can be due to inhibition, rather than, stimulation of the NMDAR by the anti- NMDAR antibodies [5]. The presentation of patients with such diversity of symptoms predicts the involvement of different areas of central nervous system **(Table 3)**.

According to our review, tumor removal was performed in all of the 20 studies indicating tumor excision as a definitive

Table 1 Literature review showing management strategies in previously reported cases (2010-2017).

										Time of Resection
S. no	Author	Sex/Age	Antibody	Tumor Resection	Corticosteroids	IVIG	Plasmapheresis	Chemotherapy	Relapse	(Days)
1	Sameshima et al. [8]	f/17	NMDAR	+	+	-	+	-	No	27
2	Massa et al. [10]	f/38	NMDAR	+	+	+	-	-	No	33
3	Tachibana et al. [11]	f/21	NMDAR	+	+	+	-	-	No	150
4	Abdul-Rahman et al. [12]	f/25	NMDAR	+	+	+	+	+	No	29
5	Wali et al. [13]	f/29	NMDAR	+	-	-	+	-	No	NA
6	Boeck et al. [6]	f/34	NMDAR	+	+	+	+	+	No	330
7	Imai et al. [14]	f/39	NMDAR	+	+	-	-	-	No	NA
8	Braverman et al. [15]	f/12	NMDAR	+	+	+	+	+	No	NA
9	Kleyensteuber et al. [16]	f/25	NMDAR	+	+	+	-	-	No	49
10	Naoura et al. [17]	f/27	NMDAR	+	+	+	-	-	No	NA
11	Kim et al. [9]	f/15	NA	+	-	+	-	-	No	13
12	Frawley et al. [18]	f/11	NMDAR	+	+	-	+	-	No	180
13	Day et al. [19]	f/21	NMDAR	+	-	+	+	-	No	NA
14	Dulcey et al. [20]	f/20	NMDAR	+	+	+	-	+	No	90
15	Lo et al. [7]	f/21	NMDAR	+	-	-	-	-	No	450
16	kawano et al. [21]	f/20	NMDAR	+	+	+	-	-	No	42
17	Yamanaka et al. [22]	f/27	NMDAR	+	+	+	+	-	No	NA
18	Johnson et al. [23]	f/27	NMDAR	+	+	+	+	+	No	150
19	Tanyi et al. [24]	f/34	NMDAR	+	+	+	+	+	No	NA
		f/24	NNMDAR	+	+	-	+	-	No	NA
		f/53	NMDAR	+	+	+	+	+	No	NA
20	Choudry	f/17	NMDAR	+	+	+	+	-	Yes	15

Table 2 Reported presenting symptoms in previous cases PNE secondary to ovarian teratomas (2010-2017).

Presenting Symptoms	Case reports
Headache (8 studies)	12, 18, 14, 21, 22, 24, 25, 27
Auditory Hallucinations (7 studies)	11, 15, 18, 20, 17, 23, Present study
Confusion (7 studies)	12, 13, 15, 18, 21, 23, 27
Agitation (4 studies)	11, 13, 23, Present study
Short term memory loss (4 studies)	12, 20, 27, 28
Flu (3 studies)	13, 14, 17
Aggressiveness (3 studies)	11, 18, Present study
Fever (4 studies)	12, 15, 27, 26
Hypoventilation	16, 29
Seizures	16, 29
Dizziness	17, 12
Vomiting	24, 25
Disorientation	12, 17
Tremors	12, 15
Insomnia	13, 21
Hyperkinesia	16
Diarrhea	24, 25
Appetite loss	13
Hyperosmia	22
Suicidal	23
Hyperthermia	24
Hypotension	29
Dystonia	28

management option. The time from presentation of symptoms to the tumor resection varied significantly. The median time of tumor removal was 45.5 days. As per our review, patients with the longest delays in resection, showed comparatively more residual symptoms after treatment. Boeck et al. and Lo et al. [6,7] reported ovarian resections after 330 and 450 days of initial presentation respectively. Both studies reported significant impaired cognitive functions, reduced psychomotor status and parapresis of extremities [7]. Patients who had immediate tumor resection displayed a better outcome [8]. Corticosteroids were administered in 81.8% (16 studies) of cases. The preferred approach of administration was pulse therapy followed by a maintenance dose as per our review. In studies not reporting corticosteroid use, the patient prognosis was detrimentally affected. Intravenous immunoglobulin therapy was administered in 72.73% (15 studies) of cases. Corticosteroids were most commonly given in combination with IVIG (64% of cases). Isolated use of IVIG was a limited approach as per our review [9]. Plasma exchange therapy was reported in almost 59.9% (11 studies) of the cases. According to our review, plasmapheresis was usually performed in the immediate post-operative period. The use of plasmapheresis and corticosteroids only; was less frequently practiced (4 studies), however showed promising outcomes. Chemotherapy use was reported (rituximab/ cyclophosphamide) in 31.81% (7 studies) cases. However in all of these studies it was used in combination with other treatment modalities as an adjuvant therapy. The combination of corticosteroids, IVIG and plasmapheresis was used in 8 studies, reporting a

Table 3 Prognosis and functional outcomes in previously reported cases of PNE with ovarian teratomas (2010-2017).

Author	Sex/Age	Outcome
Sameshima et al. [8]	f/17	Complete recovery
Massa et al. [10]	f/38	Partial remission with no consciousness with spontaneous eye opening
Tachibana et al. [11]	f/21	Complete recovery
Abdul-Rahman et al. [12]	f/25	Partial remission with memory impairment
Wali et al. [13]	f/29	Partial remission with anterograde and retrograde amnesia
Boeck et al. [6]	f/34	Partial remission with reduced cognitive function
Imai et al. [14]	f/39	Complete recovery
Braverman et al. [15]	f/12	Complete recovery
Kleyensteuber et al. [16]	f/25	Partial remission with short term memory loss
Naoura et al. [17]	f/27	Partial remission with attention deficits
Kim et al. [9]	f/15	Complete recovery
Frawley et al. [18]	f/11	Complete recovery
Day et al. [19]	f/21	Patient expired (cardiac arrest)
Dulcey et al. [20]	f/20	Complete recovery
Lo et al. [7]	f/21	Partial remission with dyskinesia, dysarthria, cognitive impairment
Kawano et al. [21]	f/20	Complete recovery
Yamanaka et al. [22]	f/27	Partial remission
Johnson et al. [23]	f/35	Complete recovery
Tanyi et al. [24]	f/34	Complete recovery
	f/24	Partial remission with amnesia and dyskinesia
	f/53	Partial remission
Choudry	f/17	Partial remission with memory and cognitive impairment after relapse

complete recovery in 50% of the cases. According to our review different treatment modalities, in variable combinations, showed indefinable results. To the best of our knowledge, neuropathological mechanisms behind this variation are still unknown. It can be due to variable NMDA receptor expression; diversity of autoimmune response or variation in synaptic response to NMDA receptors [9].

Conclusion

Paraneoplastic encephalitis is a critical yet reversible illness. Our comprehensive review and experience can be summarized in the following guidelines signifying the current clinical practices regarding PNE with ovarian teratoma. (I) PNE should be suspected in female patients presenting with an acute history of neuropsychiatric symptoms. (II) Tumor resection should be performed earliest to improve patient outcomes.(III) Administration of plasma exchange therapy in immediate post-operative period is recommended. (IV) Pulse therapy preceding intravenous immunoglobin therapy improves patient prognosis. (V) Patients should be discharged on maintenance dose of corticosteroids. (VI) Long term follow up is recommended to monitor for relapses.

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