ORIGINAL ARTICLE

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME IN CANCER PATIENTS

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ABSTRACT

Objective: To determine the demographic, clinic-radiological characteristics, the outcomes and close association of chemotherapeutic agents causing Posterior reversible encephalopathy syndrome (PRES) in cancer patients.

Material & Methods: A retrospective study was conducted at the Shaukat Khanum Memorial Cancer Hospital & Research Centre. Data of the cancer patients who developed PRES from June 2008 to June 2018 was retrieved. A total of 32 patients' were identified and the pertinent information was recorded in predesigned proforma which included information on demographics, clinical features, drug use, management and outcome. SPSS version 20 was used for simple descriptive analysis.

Results: Of the total 32 patients, 20 (62.5%) were male. Out of total subjects, the diagnosis in majority of cases was lymphoma (n=13, 40.6%). oOher diagnoses included leukemia (n=9, 28.12%), 3 (9.37%) patients had germ cell tumor and 2(6.25%) had rectal carcinoma. All the patients received chemotherapy prior to developing PRES. Half of the patients (50%) received vincristine. Most common clinical presentation was seizures (59.37%); hypertension in 11 (34.37%) patients. 23 patients (71.87%) recovered completely from PRES while 6 patients (18.75%) had partial resolution.

Conclusion: In the study, we observed the characteristics of PRES in cancer patients and a close association of chemotherapeutic agents causing PRES.

Key Words: Brain, Cancer, Chemotherapy, Neurology.

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INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a serious neurological disorder which is associated with the vasogenic edema of white matter.[1,2,3] PRES is progressively more recognized and reported in case reports and case series; however, the incidence is not known. Patients in all age groups appear susceptible; reported cases exist in patients as young as two years and as old as 90 years.[1]

Among other risk factors, PRES occurs in patients prescribed immunosuppressive and immunomodulatory therapies for malignancy, transplantation, rheumatologic conditions, and other indications.[3]

The neurotoxic effects of these cytotoxic therapies are well known but not completely understood. Toxic levels of medications are not required for the development of PRES. Patients may be normotensive, but the blood pressure is usually elevated above baseline. Cyclosporine is one of the most common cytotoxic therapies associated with neurologic deficits of PRES. After renal toxicity with cyclosporine, neurotoxicity is the most serious side effect,

affecting 25 to 59 % of transplant patients. Hypomagnesemia, hypocholesterolemia, the vasoactive agent, and hypertension have all been implicated in facilitating cyclosporine neurotoxicity. Though PRES is often reported with cyclophosphamide but it has been associated with other agents e.g, cisplatin, , cytarabine, doxorubicin, etoposide, gemcitabine, and vincristine.[4] The mechanism is thought to be similar and seems to be linked with the disorders of cerebral autoregulation and endothelial dysfunction.[5]

The study was conducted to determine the clinical spectrum of PRES in cancer patients, its association with chemotherapeutic agents, and if it is detected early, adequate treatment can be done and the occurrence of irreversible changes is prevented and decrease morbidity and mortality.

MATERIAL AND METHODS

A retrospective cohort study was conducted at Shaukat Khanum Memorial Cancer Hospital & Research Centre (SKMCH&RC) from January 2008 to December 2018. The data was extracted from electronic medical records, charts were reviewed and data was recorded using a structured format. All the patients diagnosed with PRES on radiological scan were included in the study. Patients having similar presentations but not having PRES on the radiological scan were excluded. Information on demographics like age, gender, address, clinical features, laboratory investigations, complications, clinical outcomes and discharge summaries were noted. 32 cancer patients diagnosed with PRES undergoing chemotherapy were included via non-probability convenient technique. Descriptive statistics was used for both categorical and numerical variables. SPSS V 20 was used for statistical analysis. The research ethical approval was given by the Institutional review board of SKMCH&RC.

RESULTS

A total of 32 patients were identified based on our inclusion and exclusion criteria during the study period. Of the 32 patients, 20 (62.5%) were male while 12 (37.5%) were female, with a mean age of 10 years (3-72). All of them had active cancer at the time of diagnosis of PRES. Among those, 10 patients had solid tumors While 22 had hematological malignancies with 13 (40.6%) lymphoma and 9 (28.12%) leukemia patients. Hypertension was present in 11(34.37%). The median time taken from cancer diagnosis to development of PRES was 3 months (1–24 months). (Table 1)

Table 1: Characteristics of the study participant

Characteristics	N (%)
Gender	
Male	20 (62.5)
Female	12 (37.5)
Age, median (range)	10 (3–72)
Cancer diagnosis	
Solid Tumors	
Rectal	2 (6.25)
Germ cell tumor	3 (9.37)
Choriocarcinoma	1 (3.12)
Esophageal	1 (3.12)
Ovarian	1 (3.12)
Peri-Ampullary	1 (3.12)
Ewing Sarcoma	1 (3.12)
Hematological	
Lymphoma	13 (40.6)
Leukemia	9 (28.12)
Time taken from diagnosis of cancer to development of PRES, months, median	3
Medical Comorbidity	
Hypertension	11 (34.37)
Brain irradiation	8 (25)
Central Nervous System	1 (3.12)
Metastasis	1 (3.12)
Chronic Kidney Disease	1 (3.12)
Vasculitis	1 (3.12)
Nephrotic Syndrome	1 (3.12)
Fanconi Syndrome	

All the patients received chemotherapy preceding PRES. 16(50%) of total cases received vincristine, either as single agent (n = 2) or with other agents in combination (n = 14). Other common chemotherapies included cyclophosphamide (n = 14), methotrexate (n=12) and doxorubicin (n=10). Eight patients

received prior brain irradiation with intrathecal methotrexate. **(Table 2)**

Table 2: Chemotherapy agents used by the patients.

Agent	N (%)
Any agent	
Vincristine	16 (50)
Cyclophosphamide	14 (43.75)
Doxorubicin	10 (31.25)
Dexamethasone	6 (18.75)
Prednisolone	5 (15.62)
Methotrexate	12 (37.5)
Bleomycin	3 (9.37)
Etoposide	5 (15.62)
Cisplatin	3 (9.37)
Ifosfamide	2 (6.25)
Carboplatin	1 (3.12)
Dacarbazine	2 (6.25)
Vinblastine	1 (3.12)
Mercaptopurine	2 (6.25)
Combination regimen	
Capecitabine/oxaliplatin	2 (6.25)
Busulfan-melphalan	1 (3.12)

Symptoms had started for a median of 1 day before the radiological imaging (range: 0–3 days). Common symptoms on presentation included seizures in 19 patients (59.37%), altered mental status in 8 (25%), headache in 3 patients (9.37%), one patient had blindness (3.12%) and 1 patient developed shortness of breath (3.12%). Hypertension was present in 11 (34.37%) patients. MRI and CT of brain were obtained for imaging purpose**.**Out of 32 patients, 28 (87.5%) had changes of PRES in the posterior region and 4 (12.5%) had diffuse changes. In the 28 having posterior region involvement, 19 (59.3%) had changes in parieto-occipital region, 9 (28.12%) had in the occipital region while in 4 (12.5%) parietal, occipital and temporal regions were involved. (Table 3)

Table 3: Imaging characteristics

Characteristic	N(%)
PRES location	
Posterior	28 (87.5)
Diffuse	4 (12.5)
Site	
Parieto-occipital	19 (59.37)
Occipital	9 (28.12)
Parieto-occipital and temporal	4 (12.5)
EEG	
Regional pathology	2 (6.25)
Severe encephalopathy	3 (9.37)
Generalized epileptiform discharges	4 (12.5)
Normal findings	10 (31.25)
Complications	
Intracerebral bleed	5 (15.62)
Subarachnoid hemorrhage	1 (3.12)
Micro hemorrhage	1 (3.12)
Hydrocephalus	1 (3.12)
Venous thrombosis	1 (3.12)
Encephalitis	1 (3.12)

Nineteen patients (59.37%) had fits at presentation. EEG was done on 19 patients and the result was abnormal in 9(47.3%) Epileptogenic discharge was the finding in the majority of patients. All of the patients received anti-epileptics and the dosage was tapered accordingly. Twenty-eight cases (87.5%) had complete resolution of neurological symptoms after a median of 9 days (range: 1–184 days). Follow-up imaging was available for 28 patients (87.5%), at a median of 28 days from initial scan (IQR: 10–53 days). 23 (71.87%) patients had resolution of their initial lesions on the scans; 6 (18.75%) had partial resolution of the original PRES lesions.

Three patients (9.37%) died. Of the patients alive, 18 (56.2%) on discharge they remained on antihypertensive. The median hospital stay was 20.3 days (IQR: 8–52 days) with a median follow-up of 4 months, 16 patients expired during the course of their treatment; 13 patients were alive while 2 patients lost follow up;

median overall survival for the entire cohort was 3.8 months.

DISCUSSION

PRES also known as luekoencephalopathy syndrome was first described in 1996 in patients who were having raised blood pressure or in the patients on immunosuppressive medications.[1] Subsequent reports have been done to correlate the clinical presentation with etiology of PRES [2, 3] or with the location of the lesions.[6, 7] Mean age in our study was 10 years (3-72). As compared to a study by Kamyta et al, mean age at PRES onset was 52 ± 17.8 years, [8] while in another study by Khan et al, the average age of their patients with PRES was 7 years. [9] In our study, 22 patients with PRES had hematological malignancies with 13 (40.6%) lymphoma patients and 9 (28.12%) leukemia patients. It was in line with a study conducted by Kamiya et al. where leukemia (30 %) and lymphoma (12 %) were common diagnosis.[8] while in another study reported slight high prevalence of lymphomas (57.89) and leukemia (36.84%) compare to our result finding.[9]

Prior studies of PRES have chemotherapy as a presumed cause of PRES.[7], but have been small series limited to childhood cancers[10, 11]. All the patients in our study received chemotherapy preceding PRES. Sixteen (50%) of total cases received vincristine. Other common chemotherapies included cyclophosphamide (43.75%), cisplatin (9.37%). In a systemic review by How et al, total 70 cases involving chemotherapy-associated PRES were studied. Platinum-containing drugs, Cyclophosphamide, Hydroxydaunorubicin/Adriamycin, Oncovin/Vincristine, Prednisone/R-CHOP regimens, and gemcitabine were the agents most commonly used in patients who developed chemo-associated PRES.[12] Similarly another retrospective study by Abby et al, out of 44 cancer patients who received DA-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), 3 of their patients developed PRES after administration of the combination chemotherapy regimen.[13] A case report by Zahir et al, had PRES caused by cisplatin in non-seminomatous germ cell tumor patients.[14] While chemotherapy or other agents have been described as a potential risk factor for PRES primarily only in case reports. In our study, more than half of the cases had undergone chemotherapy in the month preceding PRES, and other cases were on combination therapy. The most commonly used drug was Vincristine, either used as monotherapy or in combination.

Most common clinical presentation in our study was seizures (59.37%), this was on par with a study conducted by Kamya et al reported seizures in (67 %).[8] In another study by Musioł et al, the main symptom of PRES in their patients was headache (87.5%) and seizures (75%).[15]

Hypertension was the most common risk factor in our study associated with the development of chemotherapy-associated PRES. It was in line with a study done by How et all, where PRES was associated with hypertension in (90%) patients.[12] while in another study by Khan et al, 84.25% patients developed hypertension with PRES.[9]

In contrast to other studies, in which permanent neurologic deficits including epilepsy reported in 12%–33% children with PRES [16, 10, 11], most of the patients in our study were successfully tapered off anti-epileptics medications. There was no significant association between degree of blood pressure with location of the PRES or tumor type. Studies have found no such correlation.[10, 11] In our study, it was observed that blood pressure had improved and normalized in few of the cases by the time the causative agent had stopped. PRES caused by chemotherapeutic and immunosuppressant medications should be managed with antihypertensive, control of seizure and removal of the cytotoxic drug is usually recommended for the treatment in cases of PRES.[17] The limitation of our study was the loss of follow up in a few cases. Our effort to link specific chemotherapeutic agents with PRES may have been limited by a small number of populations as well.

CONCLUSION

Chemotherapy agents although uncommon may cause PRES in cancer patients. Clinical presentations and radiographic finding may fluctuate and PRES can be treated in most of the cases. Anticonvulsant tapering and chemotherapy re-challenge is often possible. Overall, early recognition of the offending agents, optimal treatment and blood pressure control are still the main goals to manage PRES.

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