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Research Article

Reversible Posterior Leukoencephalopathy Syndrome in Patients Undergoing Chemotherapy for Solid Tumors. A Case Report and Review of the Literature

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Abstract

Introduction: Reversible posterior leukoencephalopathy syndrome (RPLS) is a clinical entity of subtle onset of headaches, seizures, impaired vision and usually acute hypertension associated with characteristic neuroimaging findings of subcortical oedema affecting the posterior cerebral circulation. In the last two decades the causative relationship of cytotoxic and targeted antineoplastic agents with RPLS is increasingly recognized among cancer patients.

Material and Methods: Herein we present a case of advanced gastric cancer that developed RPLS after treatment with the combination of chemotherapy and Trastuzumab. A comprehensive review of the English literature and the association of cytotoxic agents used in the treatment of solid tumors, with RPLS is analyzed.

Results: 65 cases, median age 54.2 years, mainly female (83%) developed RPLS after chemotherapy-based treatment. Colorectal and lung cancer was the most frequent diagnosis, while platinum and gemcitabine based treatment was commonly related with the syndrome. Hypertension, seizures, headache and visual disturbance were the usual presenting symptoms. In the majority of the cases symptoms improved partially or completely in average in average 6.5 days after conservative management. Complete radiologic resolution of the symptoms was observed in 4.2 weeks in 57,5% of the cases and partial improvement in 2.6 weeks (42,5% of the cases).

Conclusions: Combination or single-agent chemotherapy as well as novel anticancer drugs are associated with RPLS. Clinicians need to have a high index of suspicion and the combination of the clinical picture with the characteristic neuroimaging findings can help in the prompt diagnosis. RPLS can be reversible with appropriate supportive treatment and discontinuation of the causative factors.

Keywords: Reversible posterior leucoencephalopathy (RPLS); Posterior reversible encephalopathy syndrome (PRES); Magnetic resonance imaging; hypertension; Chemotherapy.

1. Introduction

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a clinical condition characterized by headaches, seizures, impaired vision, acute hypertension and characteristic neuroimaging findings, especially posterior cerebral white matter edema [1]. It was initially described as a syndrome in 1996 and since then this clinical entity has been increasingly reported in the literature. Nevertheless, the lack of specific diagnostic criteria makes the identification of the syndrome a clinical challenge. Moreover, in the literature RPLS and Posterior reversible encephalopathy syndrome (PRES) are used interchangeably, highlighting the lack of consensus in the description of this clinical entity.

RPLS has been related with a variety of clinical conditions including malignancy and antineoplastic agents (Table 1) [1-13] . Herein we present a case of RPLS in a patient with gastric cancer treated with combination of chemotherapy and Trastuzumab. A comprehensive review of the literature in the relation of RPLS and chemotherapeutic agents in solid tumors is further performed.

1. Hypertensive encephalopathy [1]
2. Immunosuppressive treatment - Cyclosporine A[2] - Interferon-alpha [1]
3. Antineoplastic agents - Cisplatin and other platinum-based agents [3] - Gemcitabine[4] - Bevacizumab and targeted agents[5]
4. Renal diseases - Acute or chronic renal diseases[6]

- Thrombotic thrombocytopenic purpura[7] - Hemolytic and uremic syndrome[8]
5. Infection/sepsis/shock [9, 10]
6. Autoimmune disease - Systemic lupus erythematosus[11] - Systemic sclerosis[12] - Wegener's granulomatosis[12]
7. Dexamethasone[13]

Table 1: Medical conditions associated with reversible posterior leukoencephalopathy syndrome.

2. Case Report

We report a case of a 58 year old woman, initially treated with partial gastrectomy (Billroth II) and adjuvant chemoradiotherapy [14] for a for a poorly differentiated, intestinal type gastric adenocarcinoma stage IIIA ($pT_2N_3M_0$). Ten months after treatment completion the patient relapsed both locally and systemically with bilateral lung metastases. Immunohistochemistry confirmed Her 2 positive (3+) staining and the patient started on first line chemotherapy with modified DCF regime (Docetaxel 40 mg/m^2 on day 1, Cisplatin 40 mg/m2 on day 1 and 5FU 400 mg/m^2 bolus on day 1 and followed by 1000 mg/m^2 continuous infusion over 24 hours daily on days 1 and 2, repeated every 14 days) in combination with trastuzumab (6 mg/kg body weight as loading dose on day 1 and after 4 mg/kg body weight on day 1 repeated every 14 days). On day ten post cycle two, she presented at the Emergency Department of our Hospital with tonic-clonic epileptic seizures and throbbing headache. The physical examination was unremarkable while the neurological examination did not reveal any focal deficit. The main clinical and laboratory findings were normal, besides an elevated blood pressure of 177/94 mmHg and respiratory alkalosis from the arterial blood gas. MRI of the brain followed which revealed bilateral subcortical oedema at the occipital and parietal lobes (Figure 1). There were no signs of brain metastases, hemorrhage, or vascular infarction. Lumbar puncture was performed to exclude leptomeningeal disease and/or infection. The cerebrospinal fluid examination was normal (normal physical characteristics, no cancer cells present, normal biochemistry, negative microscopic examination tests for HSV1, HSV2, CMV and EBV). The clinico-radiographic diagnosis was consistent with RPLS. Patient was treated symptomatically with gradual improvement of her mental status, without any residual deficit. Brain MRI performed 4 weeks after this episode revealed that the subcortical edema had resolved (Figure 2). The patient decided against any further chemotherapy and she was offered palliative care support.

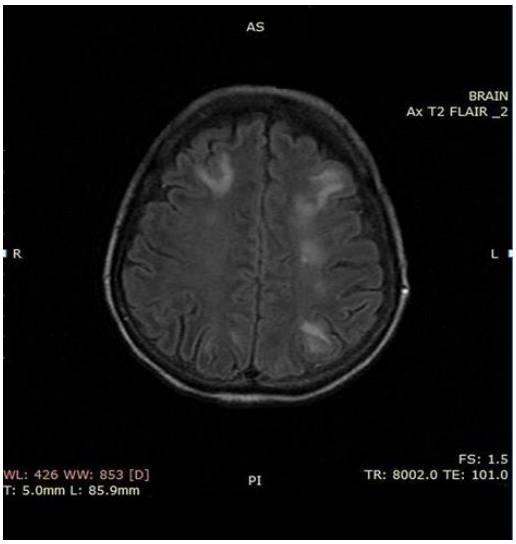

Figure 1: Magnetic resonance images of the brain showing diffuse lessions of abnormal magnetic signal mainly in subcortical white matter and in both cerebral hemispheres.

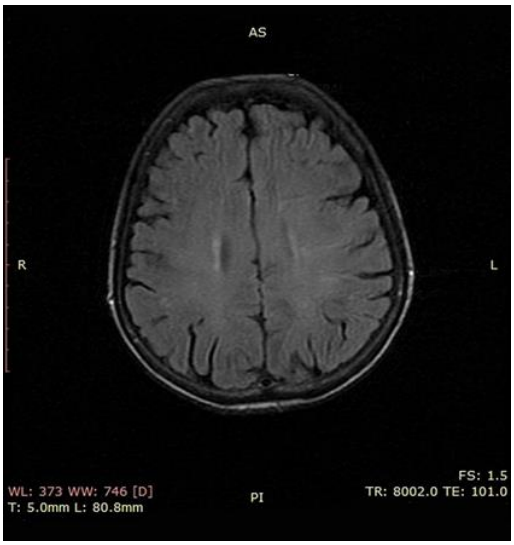

Figure 2: Follow up MRI of brain 4 weeks later showing complete response of pathological lesions.

3. Methods

We searched MEDLINE for papers using the following key words: "reversible posterior leucoencephalopathy syndrome", "posterior reversible encephalopathy syndrome", "cancer", "malignancy", and "chemotherapy". Reference lists in the retrieved papers were checked to identify any other published data. Cases were included if there was both clinical and radiological evidence of RPLS, related to chemotherapeutic agents used to treat solid tumors. Only papers written in English language and cases

with patients older than 16 years were included in the analysis. Data about the primary tumor, the chemotherapeutic agents used and the intention of the treatment, the age, gender, presenting symptoms and the number of cycles given before the development of the symptoms as well as the clinical and radiologic outcome were analyzed.

To find out if there is any correlation regarding differences between the two independent groups (males vs. females) and blood pressure in patients presented with RPLS we used Mann–Whitney test to compare them. Inferences were made at the 0.05 level of significance with no correction for multiple comparisons.

4. Results

Table 2 [3, 4, 15-67] summarizes the 67 cases, including ours, that were identified in the literature review for patients experiencing symptoms of RPLS when they were exposed to chemotherapy drugs with or without the combination of monoclonal antibodies (bevacizumab [17, 18, 22, 25, 27, 28, 37-39, 46, 51, 52, 55, 56, 58, 59, 63], trastuzumab [45, 65] or zib-aflibercept [60]) or Tyrosine Kinase Inhibitors (pazopanib [63] or erlotinib [4]). Table 3 depicts the drugs that are commonly related with the syndrome. Of the 57 cases where the treatment intention could be assessed, 46 patients (81%) were treated with palliative chemotherapy [4, 15, 17, 18, 20-25, 27-38, 41-46, 49, 51-53, 55-62, 64, 66], 9 patients had adjuvant chemotherapy [16, 19, 26, 39, 40, 47, 48, 54, 65], one neoadjuvant [67] and one treated with curative intent for testicular cancer [50]. Colorectal adenocarcinoma was the most frequent tumor type (n=19) [17, 18, 20, 22, 25, 28, 29, 37, 39, 43, 53, 54, 57-59, 61, 63, 64], followed by lung cancer (n=14; 11 NSCLC [15, 23, 24, 48, 51, 56, 60, 63, 67], 3 SCLC [31, 47, 66]), breast (n=5) [27, 44, 49, 52, 65], pancreatic (n=5) [4, 35, 40, 51, 63], urothelial bladder cancer (n=3) [21, 36, 41], sarcomas (n=3) [3, 42, 63], ovarian (n=4; 2 adenocarcinomas [54, 63] and 2 germ cell tumor (GCT) [16, 19]), gastric cancer (n=3) [34, 45], melanoma (n=2) [62, 63], glioblastoma (n=1) [38], fallopian tube (n=1) [26], cervical (1) [33], intraperitoneal mesothelioma (n=1) [30], cholangiocarcinma (n=1) [46], gall bladder (n=1) [32] and non-seminomatous GCT (n=1) [50].

In 37 cases, chemotherapeutic agents were used alone while in the rest 29 cases they were combined with targeted agents, mainly bevacizumab (Table 3). Gemcitabine was the most common agent as a single drug to cause RPLS. Platinum compounds were the most common drugs to be related with RPLS (26/37 cases), especially cisplatin (14/37). Gemcitabine was the second most common drug (12 cases) but in 7 cases it was combined with a platinum agent. In the majority of the cases (67.8%) the syndrome did appear in the first 3 cycles and in almost half of the cases (49%) in the first 2 cycles of treatment. There was a wide range though when the syndrome could present, varying between 1 and 14 cycles.

Patient no.	Primary tumor site	Treatment Intention	Regime	Age/ Gender	cycle	presenting symptoms	Presenting BP (mmHg)	Response (clinical, radiological)	References
1	Osteosarcoma	N/A	Cisplatin (intra-arterial injection)	70/M	2	generalized seizure, hyperreflexia, lethargy	180/100	cl.:N/A-CR MRI: 6w-CR	Ito et al.[3]
2	NSCLC	Palliative	Gemcitabine	55/F	5	headache, increasing somnolence, generalized tonic-clonic seizures	140-170/ 90-100	cl.:PR-9d MRI:PR-2w	Russell et.al. [15]
3	GCT of the ovary	Adjuvant	PVB	31/F	2	grand mal seizure, blurred vision	140/100	cl.: 9d-CR MRI: 2w-CR	Sueblinvong et al. [16]
4	CRC	Palliative	FOLFOX/Bevacizumab	52/F	4	bilateral loss of vision, headache, confusion	168/88	cl.: 3d-CR MRI: N/A	Ozcan et al.[17]
5	CRC	Palliative	FOLFIRI/Bevacizumab	52/M	1	headache, cortical blindness	140-150	cl.: 10d-CR MRI: 5d-PR	Allen et.al. [18]
6	GCT of the ovary	Adjuvant	PVB	17/F	5	cortical blindness, nausea, vomiting, headache	160/110	cl.: few days – CR MRI: N/A	Manchana et al.[19]
7	CRC	Palliative	FOLFOX	19/F	4	tonic-clonic seizures, lethargic	170/110	died	Skelton et.al. [20]
8.	Urothelial Bladder Ca	Palliative	Gemcitabine/Oxaliplatin	62/M	6	generalized epileptic seizures, abnormal mental status	160/90	died	Moris et.al. [21]

9	CRC	Palliative	XELOX/Bevacizumab	62/F	1	seizure	190/88	cl.: 4d-CR MRI: 10d-CR	Pinedo et al. [22]
10	NSCLC	Palliative	Cisplatin/Gemcitabine	50/F	2	headache, generalized seizure, confusion	184/92	cl.: 14d-CR MRI: CR-NA	Connolly et al.[23]
11	NSCLC	Palliative	Cisplatin/Gemcitabine	53/F	5	Headache, cortical blindness, generalized seizure	N/A	cl.: few days-CR MRI: 4w-CR	Vieillot et al. [24]
12	Pancreatic	Palliative	Gemcitabine/Erlotinib	65/F	3	disorientation, alter mental status	120-150/90-60	death due to respiratory failure	Rajasekhar et.al. [4]
13	CRC	Palliative	FOLFOX/Bevacizumab	68/F	6	blindness	140/70	cl.: N/A-CR MRI: 4w–PR & 7w-CR	Peter et al. [25]
14	Fallopian tube	Adjuvant	Intravenous Paclitaxel/ intraperitoneal Cisplatin	64/F	1	lethargy	160/93	cl.: 4d-CR MRI: 2w-CR	Onujiogu et al. [26]
15	Breast	Palliative	Doxorubicin/Bevacizumab	33/F	3	headache	150/100	cl.: 1d-CR MRI: 4d-PR	Burki et.al. [27]
16	CRC	Palliative	FU/LV/Bevacizumab	55/F	14	lethargy, tonic-clonic seizure, dysarthria	190/120	cl.: 2d-PR MRI: 7d-PR	El Maalouf et.al.[28]
17	CRC	Palliative	FOLFOX	59/M	1	status epilepticus	156/98	cl.: 1d-CR MRI: 2w-PR	Sharief and Perry [29]
18.	Intraperitoneal mesothelioma	Palliative	Cisplatin/ Pemetrexed,	32/F	7	seizures, dizziness and forgetfulness	112/85	cl: CR-7d MRI: CR-1m	Nguyen et.al. [30]
19	SCLC	Palliative	Carboplatin/ Gemcitabine	45/F	2	blurring, headache	126/84	cl.: 7d-PR MRI: 2w-PR	Bhatt et al. [31]

20	Gallbladder	Palliative	Cisplatin/Gemcitabine	58/F	3	Headache, dizziness, tonic-clonic seizure	170/90	cl: N/A-CR MRI:10d-CR	Kwon et.al [32]
21	Cervical	Palliative	Cisplatin/5-Fluorouracil	57/F	1	nausea, lethargy and reduced appetite.	N/A	N/A	Chue et.al. [33]
22	Gastric	Palliative	FOLFOX	52/F	10	generalized tonic clonic seizure	166	cl: CR – 12d MRI: PR – 1.5m	Kim et.al. [34]
23	Pancreatic	Palliative	Gemcitabine	55/F	2	nausea, vomiting, headache, cortical blindness, generalized tonic–clonic seizure	240/120	cl: PR – 4d MRI: N/A	Han et.al. [35]
24	Urothelial Bladder Ca	Palliative	Cisplatin/Gemcitabine	50/M	2	semicomatose	N/A	cl.: 14d-PR MRI: 4w-PR	Maeda et al [36]
25	CRC	Palliative	FOLFOX/Bevacizumab	63/F	10	headache, drowsiness, visual disturbance	N/A	cl.: 1w CR MRI: N/A	Lau and Paunipagar [37]
26	Glioblastoma	Palliative	Temozolomide/Bevacizumab	46/F	4	right-sided weakness, aphasia	201/117	cl.: 2d-PR MRI: 1w-PR	Lou et.al. [38]
27	CRC	Adjuvant	Capecitabine/bevacizumab	70/F	1	left-sided weakness	112/63	cl: CR – N/A MRI: CR – 6w	Lewis-Hanna et.al [39]
28	Pancreatic	Adjuvant	Gemcitabine	74/F	3	tonic-clonic seizure and visual blurring	170/90	cl: CR – 4d MRI: CR – 2w	Marrone et.al. [40]
29	Urinary Bladder	Palliative	Vinflunine	67/F	1	generalized tonic-clonic seizure	>190	cl: PR – 4d MRI: PR – 4d	Helissey et.al. [41]
30	Leiomyosarcoma	Palliative	Gemcitabine	36/F	4	lethargy, nausea, vomiting, visual	200/120	cl: N/A MRI: CR - 5w	Cioffi P et.al. [42]

						disturbances, and a lipothymic episode			
31	CRC	Palliative	XELOX	60/M	1	nausea and vomiting, tonicclonic seizures	200	Died	Femia et.al. [43]
32	Breast	Palliative	TACE: doxorubicin	63/F	1	nausea, vomiting, mental status change, generalized seizures	130/90	cl: N/A MRI: CR –8w	Pawar et.al. [44]
33	Gastric	Palliative	Cisplatin/Capecitabine/ Trastuzumab	54//F	4	vision loss	156/110	cl.: N/A MRI: N/A	Kaneda et al. [45]
34	Cholangiocarcinoma	Palliative	Gemcitabine/Oxaliplatin Bevacizumab	45/F	13	headache, generalized tonic–clonic seizure	194/112	cl.: CR-few days MRI: 10w-CR	Chang et al. [46]
35	SCLC	Adjuvant	Carboplatin/Etoposide	69/F	1	headache	80/40	cl.: 1d-CR MRI: 1w-CR	Ryan et al. [47]
36	NSCLC	Adjuvant	Carboplatin/Gemcitabine	62/M	3	heaviness of the head, ptosis of the right mouth angle	150/94	cl.: 14d-PR MRI: PR-1m	Imai et.al. [48]
37	Breast	Palliative	Cisplatin /Vinorelbine	34/F	1	headache, dizziness	170/107	cl.: 3d-CR MRI: N/A	Chen et.al. [49]
38	NSGCT	Curative	BEP	23/M	1	tonic-clonic seizure	150-170/110-100	cl.: 2d-PR MRI: 3m-CR	Zahir et.al. [50]
39	NSCLC	Palliative	Paclitaxel/Carboplatin Bevacizumab	68/F	3	headache, confused	221/84	cl.: improved MRI: 8d-CR	Seet et.al. [51]

40	Pancreatic	Palliative	Gemcitabine/Oxaliplatin Bevacizumab	63/F	1	generalized seizures, visual disturbance	190/94	cl.: 1d-CR MRI: 1m-CR	Seet et.al. [51]
41	Breast	Palliative	Paclitaxel/Bevacizumab	72/F	2	nausea, vomiting, and blurred vision	150/100	cl.: 7d-CR MRI: 4w-CR	Sclafani et.al. [52]
42	CRC	Palliative	FOLFOX	73/F	3	occipital headache, tonic-clonic seizures	198/105	cl.: 10d-CR MRI: NA	Truman et.al. [53]
43	CRC	Adjuvant	Capecitabine	62/M	1	fatigue, dysarthria	70/46	cl.: 9d-CR	Endo et.al. [54]
44	Ovarian	Palliative	Paclitaxel/Bevacizumab	31/F	2 mon. after	generalized tonic–clonic seizure	N/A	cl.: 6d-PR MRI: 6d-PR	Abas et al. [55]
45	NSCLC	Palliative	Cisplatin/Gemcitabine/ Bevacizumab	41/F	7	grand mal seizures, nausea, vomiting, limb ataxia, visual hallucinations, confusion, severe headache	245/140	cl.:PR-N/A MRI:PR-5w	Dersch et.al. [56]
46	CRC	Palliative	FOLFOX	27/F	2	Abdominal pain, vomiting, and suspect of intestinal obstruction, seizures	200/120	cl: CR-10d MRI: CR-10d	Porcello Marrone et.al [57]
47	CRC	Palliative	XELOX/ Bevacizumab,	66/M	3	blurred vision, gait disturbance, dysarthria, generalized seizures	162/99	cl: N/A MRI: N/A	Goto et.al. [58]
48	CRC	Palliative	FOLFIRI/ Bevacizumab	56/F	3	coma	123/81	cl.: 4d-CR MRI: 6d-PR	Wang et al.[59]

49				58/F	8	-	225/135	cl.: 6d-PR MRI: 6d-PR	
50	NSCLC	Palliative	Cisplatin/ Pemetrexed/ Ziv-aflibercept/	38/F	1	slurred speech, seizure, headache	N/A	N/A	Chen et.al.[60]
51		Palliative		51/F	4				
52		Palliative		72/F	4				
53	CRC	Palliative	FOLFIRI	45/F	1	headache, grand mal seizure	140-150/100	Died	Plavetic et.al. [61]
54	Uveal melanoma	Palliative	TACE: doxorubicin	56/F	1	aphasia, bilateral blurry vision, dysarthria, dysmetria	180/113	cl: CR-1d MRI: N/A	Kistler et.al. [62]
55	Melanoma/NSCLC	N/A	Cisplatin, etoposide	67/F		N/A	N/A	N/A	Fitzgerald et al[63]
56	Ovarian carcinoma		Cyclophosphamide Bevacizumab,	70/F					
57	Sarcoma		Isosfamide	33/F					
58	Melanoma		Paclitaxel/Pazopanib	48/F					
50	Pancreatic		Gemcitabine	67/F					
60	CRC		FOLFOX/Bevacizumab,	53/F					
61	mCRC	Palliative	XELOX	81/M	1	altered mental status and drowsiness	140/85	cl: CR-2w MRI: CR-2w	Tang et.al. [64]

62	Breast	Adjuvant	TCH	64/F	1	generalized seizure	200	cl: CR-2w MRI: CR-2w	Ladwa et.al. [65]
63	SCLC	Palliative	Paclitaxel/Carboplatin	60/F	3	generalized tonic–clonic seizure	190/100	cl.: 10d-PR MRI: 3w-PR	Kandemir et.al. [66]
64	NSCLC	Neoadjuvant	Cisplatin/Pemetrexed	65/F	3	confusion, tonic-clonic seizures, fever, abdominal pain, headache	137/89	cl: 10d - PR	Xie et.al. [67]
65	Gastric	Palliative	DCF/Trastuzumab	58/F	2	seizure, headache	177/94	cl.:CR-7d MRI:CR-4w	current case

Table 2: Patients with RPLS after chemotherapy. BP: Blood Pressure; M: Male; cl: clinical response, N/A: Not assessed; MRI: Magnetic Resonance Imaging, CR: complete response, GCT: Germ Cell tumor; PVB: cisplatin, vinblastine, bleomycin; d: days; w: weeks; F: female; CRC: colorectal cancer, FOLFOX: 5-fluorouracil, leucovorin, Oxaliplatin, FOLFIRI: 5-fluorouracil, leucovorin, Irinotecan; PR: partial response; XELOX capecitabine, oxaliplatin; NSCLC: non small cell lung cancer; SCLC: small cell lung cancer; NSGCT: Non seminomatous germ cell tumor; BEP: bleomycin, etoposide, cisplatin; TCH – Docetaxel, Carboplatin, Trastuzumab.

Setting		**Total Nr of Cases**		
Chemotherapy alone	Number of drugs	40	Chemotherapy Drug(s)	Number of cases
	Single	11	Gemcitabine Doxorubicin (TACE) Cisplatin, capecitabine, vinflunine Ifosfamide	5 2 1 each
	Doublet	24	Platinum /gemcitabine 5-FU/Oxaliplatin (folfox or xelox) Platinum /Etoposide Platinum /Paclitaxel Cisplatin/Vinorelbine FOLFIRI, Cisplatin/5-FU Cisplatin/Pemetrexed	7 7 2 2 2 1 each
	Triple	3	PVB BEP	2 1
Chemotherapy with Targeted agents	Targeted Agent	29	Chemotherapy Drug(s)	Number of cases
	Bevacizumab	20	5-FU/Oxaliplatin (folfox or xelox) FOLFIRI Platinum /gemcitabine Carboplatin/paclitaxel Paclitaxel 5-FU Cyclophosphamide, Irinotecan Doxorubicin Temozolomide	6 2 3 1 2 2 1 each
	Trastuzumab	3	Docetaxel/Carboplatin Cisplatin/capecitabine, Docetaxel/Cisplatin/5-FU	1 1 1
	Zib-Aflibercept	3	cisplatin/ pemetrexed	3
	Erlotinib	1	gemcitabine	1
	Pazopanib	1	paxlitaxel	1

Table 3: Chemotherapy drugs related with RPLS.

There was a significant prevalence of female patients presenting with the syndrome (Table 4). Indeed, 83% of the cases were women with median age of 53.3 years (range 17-74 years) while the median age of the 11 men was 58.8 years (range 23-81). In the majority of the cases patients presented with elevated blood pressure (BP). Systolic pressure higher than 140 mmHg and/or diastolic pressure higher than 90 mmHg was regarded as hypertension [68]. 44 of the 51 patients (86.3%) with recorded BP, presented with elevated BP. The mean systolic BP was 166.9 mmHg and the mean diastolic was 96.8 mmHg. There was no difference in BP between males and females (Table 4).

No. patients	65
Males (%)† Females (%)	11 (16.9) 54 (83.1)
Mean age, years (SD)	54.2 (±14.5)
Male (n =11) ‡ Female (n = 54)	58.8 (±14.5) 53.3 (±14.5)
Mean systolic blood pressure, mmHg (SD)	166.92 (±35.1)
Males § Females	153.8 (±34) 170.1 (±35)
Mean diastolic blood pressure, mmHg (SD)	97.1 (±19.06)
Males¶ Females	90.25 (±19.35) 98.53 (±18.94)

Table 4: Clinical characteristics of patients presented with RPLS. †P <0.05 for gender difference with binomial test assuming 50% were women. ‡ No mean age difference between men and women (P = 0.314) (Mann–Whitney test). §No difference in systolic blood pressure between men and women (P = 0.225) (Mann–Whitney test). ¶No difference in diastolic blood pressure between men and women (P = 0.384) (Mann–Whitney test.).

The presenting symptoms and the frequency of RPLS are summarized in Table 5. Although in the majority of the cases the symptoms improved after conservative management, 2 patients unfortunately died in 2 [43] and 3 [61] days after initial admission while three more patients were reported to die in a matter of few days to weeks post presentation due to general deterioration and disease progression [4, 20, 21]. In 23 case (63.9%) of the cases symptoms resolved completely in average of 6.5 days while in 36.1 % of the cases the symptoms partially resolved in 6.4 days. The radiologic resolution of the symptoms was assessed in 40 cases. In 23 cases (57.5%) there was complete resolution in MRI in 4.2 weeks, while in the rest 17 patients (42.5%) the MRI findings partially regressed in 2.6 weeks.

Presenting Symptoms	Frequency
Seizures	55.4%
Headache	37.5%
Visual disturbance	30.4%
Altered mental status	23,2%
Nausea/vomiting	16.1%
Speech disturbances	12.5%
Lethargy	8.9%
Coma/ semicomatose	3.6%
Abdominal pain	3.6%
Weakness	3.6%

Table 5: Presenting Symptoms of RPLS.

5. Discussion

RPLS is an increasingly recognized clinical syndrome related with a variety of clinical conditions and medications (Table 1). The pathophysiologic mechanisms underlying the syndrome are poorly understood, but it appears to be related to disordered cerebral autoregulation and endothelial dysfunction leading to the characteristic cerebral oedema seen in T2-weighed MRI imaging [1, 69] . This also explains the observation that platinum based chemotherapy with or without antiangiogenic agents are frequently related with RPLS (Table 2). It is well known that platinum agents damage vascular endothelial cells, which can lead to abnormal fluctuations in blood pressure and disrupt the blood brain barrier and axonal swelling [50, 70].

To our knowledge this is the first report where RPLS is related with the combination of DCF and Trastuzumab. Nevertheless, the combination of Trastuzuamb with chemotherapy has been previously reported to cause the syndrome [45, 65]. It is difficult to assess with certainty if the monoclonal antibody itself, the chemotherapeutic agents or the combination have precipitated the event. Trastuzumab blocks tumor angiogenesis by decreasing the production of VEGF and activating antiangiogenic factors, while it can also increase the blood pressure [71]. Besides cisplatin, 5-fluorouracil has been also linked to RPLS either alone [54] or in combination with other agents [17, 18, 28, 45]. Finally, docetaxel has also been related with RPLS when it was combined with Trastuzumab and a platinum compound as in our case [65].

Our case presented with symptoms matching two of the most common clinical findings for RPLS, seizures and headache (Table 5). The brain MRI revealed the characteristic white matter oedema of the occipital and parietal lobes. Even though RPLS was high in the list of differential diagnosis, we tried to rule out other medical conditions like a stroke, demyelinating disorders, encephalitis, leptomeningeal metastases which may have similar presentation [72, 73]. Neuroimaging with MRI is crucial for the diagnosis of RPLS and lumbar puncture can be helpful to exclude any other possible causes.

The role of bevacizumab and novel targeted ant-cancer agents in the development of RPLS have been reviewed recently [5, 74]. Our scope was to review the literature considering the chemotherapy agents that seem to be related with the syndrome. To our knowledge this is the most comprehensive review including cases with solid tumors treated with chemotherapy and developed RPLS. RPLS is characterized by the combination of typical clinical symptoms (Table 5) and the characteristic neuroimaging findings. Cases where the clinical picture was quite typical for the syndrome but the CT or MRI findings were missing, were not included in the analysis [75, 76]. Another case where leucoencephalopathy was evidenced 2 months after the initial symptoms was also excluded [77]. Nevertheless, this raises the question if the lack of MRI confirmation is related to a completely different clinical entity where the findings are not expected to occur, a variant of RLPS where the brain changes may happen sometime after the clinical presentation or the need of more sensitive methods to better characterize the neuronal changes, like proton MR spectroscopy [9] and magnetic resonance angiography [78] .

In 24 cases both CT scan and MRI were used during the initial investigation. In 58% of the cases the CT scan was normal which obviously highlights that MRI should be the diagnostic imaging of choice. Nevertheless, this rate is much higher than the one observed by Singer et al. (37%) [79], and needs to be interpreted cautiously. It is well known though that MRI has higher-resolution capacity, and it has the ability to show small, focal abnormalities that cannot be seen on CT [1, 80]. It seems that a variety of antineoplastic agents have been implicated in the syndrome (Table 3). Although in the majority of the cases the medications have been administered intravenously it was interesting to find that intra-arterial [3], intraperitoneal [26] or hepatic transarterial chemoemblisation could also cause the syndrome [44, 62]. Platinum compounds, especially cisplatin, and gemcitabine, through the increased prothrombotic effect and endothelial dysfunction, were the most frequently encountered agents related with RPLS [81]. The fact that 70% of the cases presented the symptom in the initial period of the treatment may indicate that there is an inherent susceptibility of these patients to develop the syndrome.

The female prevalence of the syndrome has been observed in a previous review [82] as well as in a single institution cohort [79]. Although the exact mechanism underlying this observation is not clear, we can assume that estrogens may play a role. Estrogens have been implicated with endothelial dysfunction [83, 84] and can affect many vascular mediators, like endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), transforming growth factor β (TGF-β), cyclooxygenases [83] regulating the vascular tone [85]. Nevertheless, the interplay between the offending anti-neoplastic agent, estrogens and endothelium in the development of the syndrome needs to be elucidated.

The treatment for RPLS must be symptomatic. Control of blood pressure is important especially for the patients who present with hypertension is commonly encountered with RPLS and in this review 86% of the cases had elevated BP during admission. Nevertheless it is increasingly noticed that normotensive patients may also present with the syndrome [30, 31, 39, 47, 54, 59, 77]. Treatment with anti-epileptics should be initiated in patients with seizures but there is no clear guideline about the overall duration of treatment. This need to be decided on individual basis and it is unlikely that long term antiepileptic treatment will be needed.

Withdrawal of the offending agent seems to fully or partially reverse the symptom or and the neuroimaging findings within a period of few days or weeks, respectively. In the majority of the cases there was no rechallenge of the patients with the same agent. In the few cases where the agent were reintroduced, including bevacizumab [38], no further RPLS-related symptoms were observed [38, 50, 66]. Nevertheless, when another patient was re-exposed to bevacizumab after the initial improvement of the symptoms, he experienced again similar symptoms and the drug was permanently discontinued [58]. In Singer et al. study, 7 out of the 17 patients (41%) that were rechallenged with the same anti-neoplastic treatment did not present the syndrome [79]. None of them though had bevacizumab rechallenge while this was a combined population involving patients with hematologic and solid malignancies. In general though, there is hesitance to carry on with the treatment with the offending agent unless there is strong clinical indication [50].

6. Conclusion

RPLS is a rare syndrome which is increasingly reported in the literature. The combination of the clinical symptoms and characteristic neuroimaging findings can help in the prompt diagnosis and management of this clinical entity. Clinicians need to have a high index of suspicion and request brain MRI when the syndrome is suspected.

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