Posterior reversible encephalopathy syndrome (PRES) in mesenteric leiomyosarcoma: A case report

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ABSTRACT

BACKGROUND: Posterior reversible encephalopathy syndrome (PRES) is a syndrome characterized by headache, confusion, visual loss and seizures. Many factors influence the appearance of this syndrome, predominantly eclampsia, certain medical treatments and malignant hypertension. Diagnosed by typical transient lesions on magnetic resonance imaging.

CASE REPORT: We present a case of mesenteric leiomyosarcoma in a 52 year old woman, who had severe headache, abdominal heaviness, and hypertension. Investigations revealed a mesenteric mass and a Posterior Reversible Encephalopathy Syndrome features on brain MRI, suggesting renin secretion by the tumor, causing the patient’s symptoms.

CONCLUSION: Patient’s symptoms disappeared after resection of the tumor, suggesting a renin production cessation.

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1. Introduction

Posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome (RPLS), is a syndrome characterized by headache, confusion, visual loss and seizures. Many factors influence the appearance of this syndrome, predominantly eclampsia, certain medical treatments and malignant hypertension. The symptoms can resolve spontaneously after a period of time, although visual sequelae have been reported [2,3].

The present case details a patient with mesenteric leiomyosarcoma and liver metastases who presented with headache, hypertension and PRES. Resection of her primary and metastatic disease led to resolution of PRES and hypertension.

Our case has been reported in line with the SCARE criteria [1].

2. Case presentation

A 52 year old female presented abdominal pain and severe headaches with visual disturbances. Headaches were refractory to pain medication. Initial imaging revealed an abdominal mass and liver lesion, and surgery was recommended. She was referred to our clinic where we noted severe hypertension reaching peaks of 190/110 mmHg associated with unremitting headache. The headache was described as tension-like, starting bilaterally in the occipital region and radiating to all other regions while progressive in severity over the course of two weeks prior to presentation at our clinic. These episodes were accompanied by nausea and vomiting.

Neurological examination was non-focal. Physical examination revealed a palpable left-central abdominal mass, freely mobile in the direction perpendicular to the mesentery. The patient reported that she initially noted the mass three years prior. She denied gastrointestinal symptoms. Laboratory workup was unremarkable with normal electrolytes, coagulation, liver and renal function. The patient’s history was notable for resection of a uterine leiomyoma 14 years prior; she had four pregnancies all resulting in healthy births (children aged 16–22 years).

She was immediately treated with 5mg bisoprolol and 300mg/10mg irbesartan/amlopidine and underwent brain magnetic resonance imaging and multiphasic computed tomography (CT) of the abdomen and pelvis.

MRI revealed bilateral symmetrical occipital cortical-subcortical high T2/FLAIR signal intensity highly suggestive of PRES (Fig. 1). Abdominal computed tomography revealed a 7.3 × 5.8 cm well-circumscribed mesenteric mass located on the left believed to be related to the mesentery showing heterogeneous significant enhancement with hypodense areas. No invasion or mass effect for the adjacent structures and a 4 cm solitary lesion of the left liver consistent with metastasis from the mesenteric lesion (Fig. 2).

Medical therapy controlling hypertension led to complete resolution of headaches and repeat MRI was normal. Thus we proceeded to surgery for the mesenteric and liver lesions. Operative findings included a lesion situated within the sigmoid mesocolon.

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approximately at the level of the iliac bifurcation; all vessels to
the lesion emerged from the mesocolon, none from the retroperi-
toneum proving the mesenteric origin. It was not associated with
the colon per se. The lesion and mesentery lay laterally displac-
ing retroperitoneal structures including the left ureter laterally.
Complete resection was possible without sigmoid resection.

At the same laparotomy, intraoperative ultrasound revealed 2
left lateral liver lesions, the known larger lesion in segment II
and an adjacent smaller lesion in segment II. Lateral bissegmentectomy
was completed with widely negative margins. Intraoperative ultra-
sound revealed no other liver lesions. The character of the liver was
normal. There was no evidence of ascites, adenopathy or peritoneal
disease. The operation was completed in 2 h, with less than 20 cc
of blood loss (Fig. 3).

The postoperative course was remarkable for resolution of
hypertension. In fact, antihypertensive medications were slowly
discontinued. Headache did not recur in the immediate periopera-
tive period. The patient was discharged from the hospital the fifth
postoperative day. Multidisciplinary consensus was that absent any
residual disease, adjuvant therapy was not appropriate.

Pathology revealed a left mesenteric mass: 10 × 7 × 6.5 cm mass,
weighing 217 g, well circumscribed with smooth outer aspect, seri-
ally cut, presence of some whitish fibrillary areas with predominant
shiny grayish myxoid pattern with multifocally dilated congestive
blood vessels with hemorhagic spaces containing blood clots. and
liver 12 × 11 cm in major dimensions and 2.5 cm in maximal thick-
ness covered but at the transected area, by the capsule. It shows
paramedially a bulging grayish nodule of 3.5 cm in diameter, situ-
ated at 1.5 cm from the transected margin. Cut surface is grayish
and fibrillary with negative resection margins (Figs. 3–6).

Five months later, during a clinic visit, the patient was without
complaint; however it was noted that hypertension had recurred.
Repeat CT confirmed 2 new liver lesions – one in segment VI
and a second in the papillary process of the caudate. Staging
revealed no other disease and these were treated by percutaneous
radiofrequency ablation (RFA). Follow-up CT confirmed complete
ablation, and hypertension again improved, though briefly. Three
months post-RFA, hypertension progressed, and required escalat-
on of her antihypertensive medications. Repeat imaging revealed
fairly extensive, multifocal intrahepatic recurrence, but no extra-
hepatic disease (Fig. 7).

Absent effective chemotherapy, radioembolization was elected,
which again controlled the hypertension, but only for a few months.
Liver lesions progressed, and the family wished to attempt salvage

**Fig. 1.** Brain MRI. Arrows indicate Bilateral symmetrical occipital cortico-subcortical high T2/FLAIR signal intensity suggesting a vasogenic oedema within the occipital and parietal regions most likely relating to the posterior cerebral artery supply This confirm Posterior Reversible Encephalopathy Syndrome (PRES).

**Fig. 2.** Computed tomography: Left panel, mesenteric mass with mixed hyper- and hypo-attenuating areas on arterial phase imaging; Right panel: similar appearing lesion in segment II liver.
therapy. Systemic therapy (MAID regimen: mesna/ ifosfamide/ doxorubicin/ dacarbazine) was undertaken, with initial but short-lived clinical response. Lung lesions became evident along with hepatic insufficiency and ascites; shortly thereafter progression of one lesion in the liver compressed the duodenum creating partial gastric outlet obstruction. Palliative measures were undertaken.
and the patient died 20 months after diagnosis, about 19 months after surgery. She required anti-hypertensive therapy to control difficult hypertension until her death.

3. Discussion

Posterior reversible encephalopathy syndrome (PRES) [5,6] is a clinic-radiological pathology described based on 15 cases by Hinchey et al. [5] in 1996. Only two small case-series were reported thereafter [8,9]. It is a rare paraneoplastic condition, in this case associated with a high grade leiomyosarcoma.

Multiple names have been used to describe this condition (reversible posterior leukoencephalopathy syndrome, reversible posterior cerebral edema syndrome, and reversible occipital parietal encephalopathy). PRES is now the accepted term [5,6,10].

It has a characteristic clinical presentation with headaches, nausea/vomiting, visual disturbances leading up to decreased level of consciousness, focal neurological signs and seizure activity. It is known to have a mortality rate of 15% if untreated [11,12].

Clinical manifestations and radiological signs give the diagnosis of PRES. In doubtful cases, clinical and radiological improvement with appropriate treatment suggests the diagnosis, but there is no consensual data regarding presumptive diagnosis without radiological findings [17].
Acute hypertension is not required to cause the cerebral manifestations of PRES, though some believe that acute changes in blood pressure initiate the process of cerebral edema and subsequently the neurologic findings. Hypertension is His a central feature reported in most studies – affecting 67%–80% of patients [7–9,11,12,14,15]. Hypertension was a clear signal of tumor recurrence in our patient, and resection of the tumor led to resolution of both the hypertension and the PRES symptoms in our case.

In PRES, the triggers of acute hypertension are most often acute kidney injury or eclampsia [19,20], but hypertension is also reported in Guillain–Barré syndrome [21,22] and with drug toxicity [15]. Other reported triggers of PRES include acute/chronic hypertension, acute/chronic kidney failure, eclampsia, autoimmune disease, immunosuppressive drugs, illicit drugs (e.g. cocaine) as well as sepsis and multi-organ failure. Some chemotherapy has been associated with PRES; the only precipitating factor in our patient was the tumor (most likely the liver metastases).

Brain MRI is the most important imaging study for the diagnosis of PRES. Proton-density and T2-weighted images show high signal regions indicating edema. Fluid-attenuated inversion recovery (FLAIR) sequences also allow visualization of subcortical and corticbral lesions [7]. T1-weighted images can show low-intensity foci. Diffusion-weighted imaging (DWI) is usually normal but the apparent diffusion coefficient is elevated [16]. Overall, 50% of the cases show enhancement [14].

The four radiological patterns of PRES include holo-hemispheric watershed pattern in 23%, a superior frontal sulcus pattern in 27%, a dominant parietal occipital pattern in 22% and finally a partial or asymmetric expression of primary patterns in 28% of patients [14].

MRI should be performed either as the first or as the second imaging study; it is preferred to CT for the diagnosis of PRES [5–7,10,11,14,16].

To confirm the diagnosis radiologically, brain MRI will generally reveal bilateral symmetrical occipital and mainly subcortical high T2/FLAIR signal intensity with restricted diffusion and susceptibility artifact or contrast enhancement consistent with vasogenic edema. In some cases, and to a lesser degree, similar posterior parietal cortical changes can be seen.

The two principal hypotheses for the origin of PRES seem contradictory. One deems impaired cerebral autoregulation responsible for an increase in cerebral blood flow, whereas the other one involves endothelial dysfunction with cerebral hypoperfusion. The hypoperfusion hypothesis is more related to PRES due to drug toxicity. But the two hypotheses suggest a blood–brain–barrier dysfunction with subsequent cerebral vasogenic edema [6].

In recent years, various cases of PRES [23–32] have been reported with a supposed connection to antineoplastic drugs, which are similar in structure and action mechanism. There is a stronger association between PRES and the application of combined cytotoxic drugs compared to single drug treatment [32–34].

Monoclonal antibodies, tyrosine kinase inhibitors, fluorouracil, doxorubicin and platinum based drugs are known to trigger PRES. However a class-effect can be considered for fluorouracil, doxorubicin and platinum based drugs because of their known toxic effect: ect on the central nervous system [26,27,31,32].

A case of paraneoplastic secondary hypertension due to a renin-secreting desmoplastic small round cell tumor was reported, showing a possible link to tumors by malignant secretion of renin causing hypertension and PRES [35]. Renin was found in several organs other than the kidneys, including the brain, genitourinary tract, salivary glands, vessels, skeletal muscles and heart [35].

Furthermore, the classification for renin secreting tumors covers tumors arising from the juxtaglomerular apparatus of the kidney, renin-secreting renal tumors like Wilms’ tumor, clear cell-type renal cell carcinoma, oncocytoma and mesoblastic nephroma and finally extrarenal tumors, including granulosa cell tumors, lung cancer and pancreatic cancer and others [36–39].

Mesenteric leiomyosarcoma is believed to originate from the smooth muscle of mesenteric vessels [4]. Recurrence rates of up to 51% for abdominal disease has been reported (no recurrence was seen at the primary site in our patient) [44]. Prognosis is fairly poor with a median survival of only 12–14 months [45]. Given the correlation between tumor grade/mitotic activity of sarcomas with prognosis, it is not surprising that our patient with highly mitotically active tumor suffered liver recurrence despite complete resection of oligonodular disease found at presentation.

Forty cases of extra-renal tumors secreting renin have been reported since 1988 [35]. The diagnosis is made based on histopathologic evidence of positive immunostaining for renin or by electron microscopic identification of renin granules [40–43]. These granules could be rhomboid crystalline protogranules and amorphous homogeneous, round, electron dense mature granules [40]. Measurement of renin and immunostaining are not used in the clinical setting, which is why it was not assessed in our patient to confirm the link between the leiomyosarcoma and renin secretion causing PRES. Instead we included all possible triggers and confirmed the diagnosis by a cerebral MRI. Renin was unfortunately not measured in our patients.

In PRES the elimination of triggers should lead to remission. This includes aggressive blood pressure management which may include increased ultrafiltration, elimination of the drug responsible for the toxicity, or delivery in case of eclampsia. Steroid therapy is expected to reduce the cerebral edema, yet there is no evidence for its effect in PRES [44].

Excision of the renin secreting tumor causing PRES lead to a marked improvement of symptoms as experienced in our case after resection of leiomyosarcoma and hepatic secondaries.

4. Conclusion

It is important to recognize the significance of symptoms leading to the clinical diagnosis of PRES in cancer patients [35]. Our patient complained of headache – and rapid evaluation and treatment avoided progression of neurological symptoms. Diagnosis is suspected when some combination of headache, altered mental status, seizures and/or disturbances of vision are noted, especially in the presence of hypertension. Brain MRI usually reveals posterior cerebral white matter abnormalities seen on T2 weighted images. This simple workup may help to avoid other unnecessary diagnostic tests [2]. Furthermore, PRES is reversible by prompt lowering of raised blood pressure, and by cessation of the administration of offending immunosuppressive and cytotoxic agents [2]. In our case, resection of the offending tumor resolved the symptoms. Unfortunately this rare but aggressive tumor recurred.

Conflicts of interest

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Consent
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Author contribution
Ramy Schoucair: Study design and concept, writing the paper.
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