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Posterior reversible encephalopathy syndrome (PRES) and myeloma

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ABSTRACT

Posterior reversible encephalopathy syndrome (PRES) has rarely been described in myeloma, but chemotherapy is a known risk factor. We report 3 patients with myeloma who developed PRES, and analyzed them with 13 published cases, mostly women. The most frequent causative agents were proteasome inhibitors and autologous stem cell transplantation. Risk factors were frequently associated: hypertension, infection or renal failure. Symptoms included headache, blurred vision, altered mental status, seizures. Most patients experienced rapid clinical recovery, without relapse even after resuming treatment. Although rare, we must remain vigilant about PRES in myeloma patients. Stricter control of blood pressure could limit its occurrence.

Posterior reversible encephalopathy syndrome (PRES) is a neurological disorder characterized by a wide range of neurological symptoms such as headache, visual disturbances, focal signs, seizures, vomiting, confusion, drowsiness, and even encephalopathy [1].

The exact incidence of PRES is not well known. It has been reported between 0.4 and 6 % after solid organ transplantation, and up to 8 % following bone marrow transplantation. All age groups appear to be susceptible as reported cases exist in patients from 2 to 90 years-old, and PRES seems more common in women [1].

The brain CT is useful to exclude alternative diagnoses; it can show bilateral edema but can also be normal. Diagnosis relies on MRI, which is more sensitive and typically shows symmetrical hyperintense lesions of the white matter in the lower cerebral hemispheres, related to bilateral vasogenic edema.

These lesions are usually reversible within 2 to 4 weeks. Prognosis is thus generally good, with complete recovery for most patients. However, some severe cases may be complicated by cytotoxic edema responsible for irreversible lesions or cerebral hemorrhages. Some patients may therefore have persistent neurological deficits or epilepsy, and some cases may even be fatal.

Pathophysiologically, it has been postulated that PRES is related to a relative hypertension leading to increased capillary filtration pressure, and/or to endothelial dysfunction leading to blood-brain barrier leakage. Severe hypertension can cause secondary endothelial dysfunction. PRES can also be caused by endothelial dysfunction in patients with relatively normal blood pressure [1].

The most common causative factors are hypertension and/or rapid changes of blood pressure, fluid overload, sepsis, renal failure and uremia, eclampsia, autoimmunity, and chemotherapy or immunosuppressant treatments.

Treatment includes control of blood pressure, treatment of any infection, correction of renal failure and of any ionic or metabolic imbalance, delivery of the foetus if PRES is related to eclampsia, and transient or permanent discontinuation of the responsible drugs [1].

PRES is recurrent in about 5–10 % of cases, especially in case of uncontrolled hypertension [1]. In case of treatment-related PRES, it does not systematically recur upon re-exposure to the initial causative agent.

Many chemotherapies and immunosuppressants used to treat hematological diseases have been associated with PRES. In multiple myeloma, PRES has only been described in a few cases. It has been

Abbreviations: Asct, Autologous stem cell transplantation; ct, Computerized tomography; dd, Daratumumab, Dexamethasone; drd, Daratumumab, Revlimid, Dexamethasone; dvrd, Daratumumab, Bortezomib, Revlimid, Dexamethasone; fda, U.s. food and drug administration; kpd, Carfilzomib, Pomalidomide, Dexamethasone; mri, Magnetic resonance imaging; pres, Posterior reversible encephalopathy syndrome; VCD, Bortezomib, Cyclophosphamide, Dexamethasone; VRD, Bortezomib, Lenalidomide (Revlimid), Dexamethasone; VTD, Bortezomib, Thalidomide, Dexamethasone.

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reported with Thalidomide [2,3] but mainly with proteasome inhibitors such as Bortezomib [4–9] or Carfilzomib [10–12], and with autologous stem cell transplantation [13].

One of our patients presented a PRES that was attributed to Daratumumab. We did not find any publication on Pubmed reporting this kind of side effect of Daratumumab, however we found an FDA phase IV clinical study reporting cases of PRES in patients treated with Daratumumab [14]. In this phase IV study, 14 283 patients reported side effects when treated with Daratumumab, among who 17 patients (0.1 %) reported a PRES. These patients were mainly women (70 %), 60 years-old or older, and had been under Daratumumab treatment for 1 to 6 months.

We then sought to report cases of PRES that occurred with Daratumumab. We asked hematologists throughout France, through the FIM (Intergroupe Francophone du Myélome) cooperative group, to report any PRES that occurred in myeloma patients. We have not found any other case of PRES related to Daratumumab, but 2 other myeloma patients have presented with PRES. We present here these 3 myeloma patients with PRES.

Patients' characteristics are presented in Table 1.

PRES is a rare but not so unusual complication after chemotherapy, and during treatment of multiple myeloma. If recognized and treated promptly, the course is usually favorable with a clinical and radiological recovery that can be complete within weeks or months. However, some severe cases may be responsible for persistent neurological deficits or even life-threatening events. It therefore seems important to keep this potential complication in mind for our patients.

We only found 3 cases in France, we thus wanted to group all cases of PRES associated with myeloma or gammopathy, i.e. our 3 cases and the 13 similar published cases (Table 2). We observed that nearly all patients were female, with a mean age at PRES diagnosis of 59 years. Two patients had AL amyloidosis associated with myeloma. No case of PRES associated with POEMS syndrome has been reported to our knowledge. The number of previous lines of treatment, the time since the start of the current line of treatment, and the disease response at the time of PRES were variable, however the time between the last dose of chemotherapy and the onset of PRES was 33 days or less in all cases.

Hypertension was frequently associated, but sometimes moderate, and was not observed in all cases. It is possible that the combination of even moderately elevated blood pressure and the effects of chemotherapy contribute to the development of PRES. This may suggest that we need to be vigilant about blood pressure control in these patients. Other risk factors included infection and renal failure, the development of an infection could be a triggering factor. This point is important because our patients are frequently immunodeficient, due to their disease and treatments. No direct link has been described between immunodeficiency and PRES, but infections are known risk factors. Our patients are already usually on anti-infectious prophylaxis, are closely monitored and receive early intervention in case of fever. This approach seems also important in preventing infections-associated complications such as PRES.

Interestingly, many cases of PRES have been reported following Covid-19 infection. Mechanisms could include endothelial damage caused by Covid-19, particularly in case of cytokine storm syndrome. In addition, the virus' spike protein binds directly to the angiotensin-converting enzyme receptor 2 on the capillary endothelium, causing damage and increasing its permeability. This increased vascular permeability could be one of the reasons for the association between Covid-19 and PRES. This seems to be yet another reason to recommend vaccination against Covid-19 in our patients.

The most frequent symptoms were headache, blurred vision and altered mental status initially. Seizures were frequent but often delayed. No patient had any significant neurological history or neuropathy prior to the onset of PRES.

Regarding chemotherapy, the reported cases of PRES seem to be mainly associated with proteasome inhibitors, bortezomib [4–9] or

Table 1
Patients' characteristics, previous history, clinical findings, diagnosis, treatment and follow-up.

	Patient 1	Patient 2	Patient 3
Demographics			
Sex	Female	Female	Female
Age at myeloma / PRES diagnosis	73 / 76	62 / 64	53 / 60
Myeloma at diagnosis			
Isotype	Lambda light chains	IgA kappa + kappa light chains	IgG lambda
Renal failure	Acute renal failure requiring dialysis	Yes	No
Anemia	No	Yes	No
Hypercalcemia	No	No	No
Bone lesions	No	Yes	Yes
ISS stage	3	3	1
Extramedullary disease	Renal AL amyloidosis	No	No
High-risk cytogenetics*	No	Yes (gain 1q)	No
Previous myeloma treatment			
1st line	VCD x 6	VRD x 3, DVRD x 1, DD x 2	VTD x 4, ASCT, VTD x 2
2nd line	DRD x 4, then DD x 2	–	DRD x 20
3rd line	-	–	KPD, ASCT
Myeloma response at PRES diagnosis	Partial response	Partial response	Complete response
Myeloma treatment at PRES diagnosis	2nd line: DD (Revlimid stopped for intolerance)	1st line: Melphalan and ASCT	3rd line: Melphalan and ASCT
Time since first dose of current treatment: mean (days)	173	19	15
Time since most recent dose of treatment: mean (days)	5	19	15
Risk factors for PRES			
Hypertension	Yes	Yes	Mild hypertension
Sepsis	Covid-19 pneumopathy	Yes (catheter infection and pneumonia)	One episode of fever, no sepsis
Renal insufficiency	Yes (dialysis)	No	No
Autoimmune disease	No	No	No
Immunosuppressant therapy	No	No	No
Other	No	Mild hypomagnesemia	No
PRES symptoms	Headache, nausea, difficulty walking, confusion, drowsiness, then status epilepticus (patient found on the ground)	Headache, visual blur, vomiting, hallucinations, partial epileptic seizure	Drowsiness, confusion, fall following a possible epileptic seizure (patient found on the ground)
Imaging			
CT scan	Diffuse posterior white matter hypodensities and hemorrhagic suffusion	No CT	Normal (no hemorrhage)
MRI	Vasogenic edema of the fronto-parieto-	Bilateral occipital lesions in FLAIR hypersignal of the	Bilateral cortico-subcortical occipital,

(continued on next page)

Table 1 (*continued*)

	Patient 1	Patient 2	Patient 3
	occipital white matter with posterior predominance, minor arachnoid hemorrhages	cortex and the subcortical white matter No hemorrhage	parietal and frontal lesions in FLAIR hypersignal, bilateral thalamic involvement
PRES treatment	Initial sedation and mechanical ventilation for coma, control of blood pressure, anti-epileptic, continuation of dialysis, planned permanent discontinuation of amyloidosis/ myeloma treatment	Control of blood pressure, anti-epileptic, calcium channel blocker for hemodynamic stenosis on cerebral vasospasm, magnesium	Control of blood pressure, anti-epileptic, mannitol
Follow-up	No recurrence of hypertension nor epilepsy after discontinuation of treatment, no relapse of myeloma or amyloidosis without treatment (8 months of follow-up), continuation of dialysis, progressive neurological recovery after physical therapy	Complete clinical recovery, no neurological relapse after discontinuation of treatment, continuation of anti-hypertensive treatment (previous known hypertension), resumed myeloma treatment with Daratumumab and maintenance Revlimid	Very fast clinical recovery, no neurological relapse after discontinuation of treatment, resumed myeloma treatment with KPD

* *del(17p), t(4;14)] or gain 1q*

VCD: Bortezomib, Cyclophosphamide, Dexamethasone

VRD: Bortezomib, Lenalidomide (Revlimid), Dexamethasone

VTD: Bortezomib, Thalidomide, Dexamethasone

DRD: Daratumumab, Lenalidomide (Revlimid), Dexamethasone

DD: Daratumumab, Dexamethasone

DVRD: Daratumumab, Bortezomib, Lenalidomide (Revlimid), Dexamethasone

ASCT: Autologous Stem Cell Transplantation

KPD: Carfilzomib, Pomalidomide, Dexamethasone.

carfilzomib [10–12]. The mechanism is not yet fully understood, but it has been hypothesized that proteasome inhibitors may be responsible for a decreased transcription of certain growth factors including vascular endothelial growth factor (VEGF), which may lead to endothelial dysfunction, vasospasm, and blood-brain barrier disruption, promoting the development of PRES [10,11].

Four patients developed a PRES shortly after intensification with melphalan followed by autologous stem cell transplantation (ASCT). In the literature, the occurrence of PRES after ASCT is rare but has been previously described [13,15].

Concerning Daratumumab, 2 of our 3 patients received Daratumumab before developing a PRES. Only one developed a PRES shortly after a Daratumumab infusion. In this case, the short delay (5 days) between the Daratumumab infusion and the PRES might suggest the involvement of Daratumumab in the occurrence of PRES, but the patient had 3 other risk factors: hypertension, Covid-19 infection and chronic renal failure – causality thus remains unclear. At the time of PRES, she was no longer taking Lenalidomide due to poor tolerance. To our knowledge, no cases of PRES have been described after Lenalidomide or Pomalidomide, but 3 cases of PRES have been described in patients receiving Thalidomide [2–4]. For the second patient, who received Daratumumab but developed a PRES after ASCT, reintroduction of Daratumumab after ASCT did not lead to PRES recurrence. Because Daratumumab is rarely used alone, it is difficult to establish its exact role in the occurrence of PRES, but it may be useful to remain vigilant for this potential complication.

Table 2
Summary of our 3 cases and 13 similar published cases [2–13,15].

	Cohort: 16 patients
Demographics	
Sex female / male	15 / 1
Age at PRES: mean (range)	59 (45–76)
Hemopathy, N (%)	
Myeloma	12 (75)
Myeloma + amyloidosis	2 (12)
Plasmacytoma	1 (6)
Waldenström	1 (6)
Line of treatment, N (%)	
1	8 (50)
2	1 (6)
3	3 (19)
More	2 (12)
Missing	2 (12)
Myeloma/gammopathy response at PRES, N (%)	
CR	3 (19)
PR	10 (62)
Relapse	3 (19)
Treatment at the time of PRES, N (%)	
Thalidomide	3 (19)
Bortezomib	6 (37)
Carfilzomib	3 (19)
Melphalan low dose	1 (6)
ASCT (melphalan high dose)	4 (25)
Dexamethasone	8 (50)
Daratumumab	1 (6.25)
Time since first dose of current treatment: mean (range)	82 days (2 days – 11 months)
Time since most recent dose of treatment: mean (range)	9 days (1–33 days)
Associated risk factors for PRES, N (%)	
Hypertension	11 (69)
Infection	4 (25)
Renal failure	5 (31)
No associated risk	5 (31)
PRES symptoms, N (%)	
Headache	10 (62)
Blurred vision	8 (50)
Confusion	10 (62)
Seizure	14 (87)
CT informative / done, N	8 / 10
MRI informative / done, N	15 / 15

The role of dexamethasone is difficult to assess here, since it is almost never used alone in myeloma, and since it is known to raise blood pressure. Dexamethasone and steroids have been associated with PRES but have not been reported as the causative agent in myeloma, to the best of our knowledge.

Treatment typically included control of blood pressure, sometimes using Nimodipine (calcium channel antagonist) both for preventing the cerebral vasospasm and for blood pressure management, anti-epileptic therapy, and discontinuation of suspected causal treatment. Three patients required intubation.

14 of 16 patients experienced rapid complete clinical recovery, usually within a few days, the other 2 kept moderate neurological deficits. When repeat MRI was performed (7 patients, 3 weeks to 3 months later), it showed complete or almost complete recovery.

PRES can be recurrent, especially in case of uncontrolled hypertension. There does not appear to be any contraindication to resumption of chemotherapy because recurrence of PRES after reintroduction of causal therapy is not systematic. In these cases, no relapse of PRES was observed even after resuming treatment but no patient was re-treated with the most suspected causal molecule. Five patients died, 4 of

progressive myeloma and 1 of multiple comorbidities.

Learning points

- PRES is a rare complication but can occur in patients undergoing chemotherapy for myeloma.
- We may suggest vigilance in blood pressure control under chemotherapy and especially under proteasome inhibitor and/or autologous stem cell transplantation.
- Risk factors associated with chemotherapy include hypertension, renal failure and infections.
- Rapid diagnosis is essential, one should consider the diagnosis of PRES in a patient with headache, blurred vision or altered mental status, and prevent the onset of epileptic seizures.
- The evolution is generally favorable and reintroduction of treatment appears possible without recurrence but a switch of therapy seems generally preferred.

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Helsinki declaration

The work presented is in accordance with the Declaration of Helsinki.

Patient perspective & informed consent

All patients gave informed consent for the collection of data and the writing of this manuscript.

CRediT authorship contribution statement

Ricardos Ghanem: Conceptualization, Writing – original draft, Writing – review & editing. **Sylvie Glaisner:** Data curation, Investigation, Resources. **Arthur Bobin:** Data curation, Investigation, Resources. **Anne-Marie Ronchetti:** Data curation, Investigation, Resources. **Sophie Cereja:** Data curation, Investigation, Resources. **Bertrand Joly:** Data curation, Investigation, Resources, Validation, Visualization. **Célia Salanoubat:** Data curation, Investigation, Resources. **Guillemette Fouquet:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors have no conflict of interest related to this manuscript.

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