Posterior reversible encephalopathy syndrome secondary to oxaliplatin-based chemotherapy and regorafenib in metastatic colorectal cancer : case reports and literature review

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Abstract

Posterior reversible encephalopathy syndrome (PRES) is a rare disorder with multiple causes but potentially caused by chemotherapy. We present 3 cases of PRES of whom 2 are presumably caused by oxaliplatin and one by regorafenib. We discuss in this article the 3 cases individually and we summarize in the discussion the proposed theories in the literature of possible pathophysiological mechanisms. Our main goal of this article is to increase awareness among physicians when they are confronted with patients on chemotherapy who present with (sub)acute encephalopathy. (Acta gastroenterol. belg., **2020**, 83, **47-50**).

Key words : colorectal cancer, encephalopathy, regorafenib, oxaliplatin.

Introduction

In the last two decades, posterior reversible encephalopathy syndrome (PRES) has been increasingly recognized, but remains a very rare disorder. The exact pathophysiology is not fully understood. The syndrome is characterized by headaches, altered mental status, seizures and visual loss although clinical symptoms can be atypical (1). There are numerous factors that can trigger the syndrome such as arterial hypertension, renal failure, autoimmune disorders, eclampsia and immunosuppressive therapy and chemotherapy (2,3).

Case reports

Case report 1

A 59-year-old woman was hospitalized in 2012 because of severe nausea and vomiting since one week. Eight days earlier, she received the third cycle of adjuvant chemotherapy of mFOLFOX4 (oxaliplatin 85 mg/m², levofolinic acid 200 mg/m², fluorouracil 400 mg/m² bolus with 2400 mg/m²/46 h infusor). She was being treated for a rectal adenocarcinoma for which she already received neo-adjuvant radiotherapy (25 fractions of 1.8 Gy) in combination with capecitabine and bevacizumab fortnightly, followed by laparoscopic assisted abdomino-peritoneal rectum amputation.

Within the next hours of admission, the patient developed disorientation and confusion followed by tonic-clonic seizures. After spontaneous recovery of the seizures, a magnetic resonance imaging (MRI) of the brain revealed T2/Fluid-Attenuated-Inversion-Recovery (FLAIR) hyperintense cortico-subcortical signals in the occipital, parietal and anterior regions, compatible with PRES (Figure 1A). Ophtalmologic and additional neurologic investigation did not reveal other abnormalities. Therapy with valproic acid and levetiracetam was started.

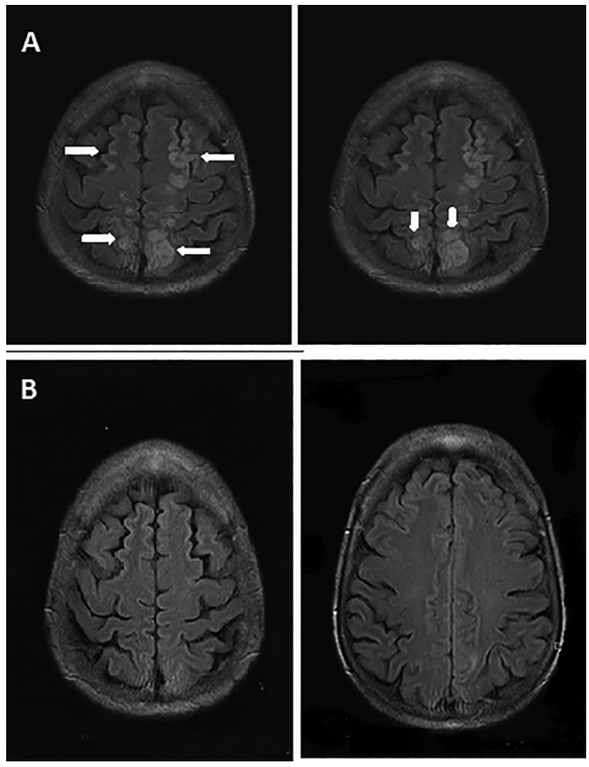

Fig. 1. — A : FLAIR hyperintense cortico-subcortical signals in the occipital, parietal and anterior regions. B : Complete resolution.

There was no prior history of high blood pressure. During this hospitalization, blood pressure was elevated but normalized quickly. Three days later, the patient

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experienced cortical blindness with denial (Anton-Babinski syndrome). These symptoms as well as the other neurological symptoms recovered completely after 10 days. A MRI performed 12 days after admission showed complete resolution of the hyperintensive signals (Figure 1B). No further chemotherapy was administered. At this moment (6.5 years after the incident), the patient is in good condition without evidence of disease recurrence, nor remaining neurological symptoms.

Case report 2

A 66-year-old patient was treated in 2015 with mFOLFOX4 for an insulin producing pancreatic neuroendocrine tumor (NET). She underwent 9 years before a distal pancreatic tail resection, splenectomy and a liver metastasectomy of segment 4b-5 and 2-3 (histological a grade 1 NET with a Ki67 of 2%). After she relapsed in 2009 with liver metastases until September 2015, she was pretreated with everolimus, somatostatine analogue octreotide, diazoxide, sunitinib and 3 times liver chemo-embolisation with doxorubicin hepaspheres. In September 2015 the patient's general condition declined and she had disease progression, mainly in the liver. At that time a treatment of chemotherapy of mFOLFOX4 was initiated.

After the third cycle of mFOLFOX4, she entered the emergency room because of general deterioration and encephalopathy. She is known with arterial hypertension since June 2015 (due to treatment with sunitinib) and chronic renal insufficiency. A computed tomography (CT) scan of the brain revealed hypodense lesions biparietal involving the white matter. MRI confirmed the diagnoses of PRES syndrome with edema occipitoparietal bilaterally (Figure 2) and meningoencephalitis was ruled out with a lumbar puncture. There was no evidence for cerebral metastases, nor meningeal carcinomatosis. Therapy with levetiracetam was initiated. Her blood pressure was monitored but there was no need for treatment. The patient made a gradual, full recovery after two weeks.

Treatment with mFOLFOX4 was stopped and the dose of octreotide was increased. With recurrence of hypoglycemia and no option for Peptide Receptor Radionuclide Therapy (PRRT), treatment with temozolomide and capacitabine was tried but patient died at the end of September 2016 due to disease progression.

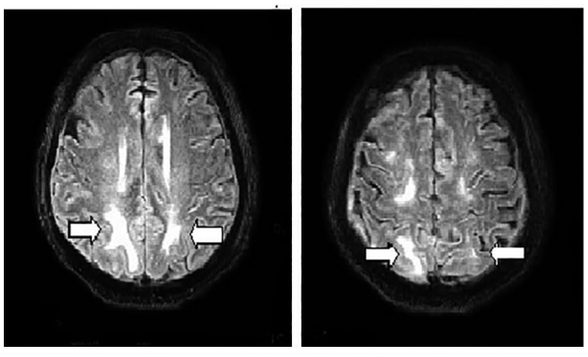

Fig. 2. — Edema occipitoparietal bilaterally on MRI.

Case report 3

A 57-year-old woman was known with a lung and liver metastatic left-sided colorectal carcinoma. She was pretreated with 5fluorouracil, irinotecan, oxaliplatin and bevacizumab from 2009 to march 2015 in different sequences with the occasionally drug holiday. Meanwhile she underwent a resection of the primary colon tumor and a right hemi-hepatectomy and a wedge excision of 3 lung metastases. After progressive disease in March 2015, she started treatment with regorafenib.

Ten days after starting regorafenib, she suffered from severe nausea, vomiting, confusion and dysarthria for 5 hours. The patient was admitted to the Emergency Room and at the arrival she had tonic-clonic seizures and elevated blood pressure of 203/89 mmHg. A brain CT scan, a full blood work up (including inflammation parameters, renal and liver function) and lumbar puncture were normal. Of relevance is that her blood pressure has always been normal until the start of regorafenib.

Brain MRI revealed a hyperintensive signal bilateral in the frontal, parietal and occipital cortex on the FLAIR phase. There was no evidence of brain metastases nor meningeal carcinomatosis.

During hospitalization the patient was treated with intravenous nicardipine, metoprolol and levetiracetam. After two days the patient had normal consciousness, good orientation and she was cooperative. She still had a mild right sided paralysis for a week with full recovery. The patient did not receive further chemotherapy and she died in March 2016 due to disease progression.

Discussion

PRES is a rare disease with severe morbidity. PRES is diagnosed if a patient presents with (sub)acute encephalopathy and the typical imaging patterns on MRI in the presence of one of the numerous triggers and the absence of underlying infectious, metabolic or malignant causes of encephalopathy (Tabel 1). The onset of clinical symptoms are acute to subacute (from hours to days) and includes encephalopathy (incidence of 50-80%), seizure (60-75%), headache (50%), visual disturbances (33%), focal neurological deficit (10-15%) and status epilepticus (5-15%) (2).

Focal regions of symmetric hemispheric edema in the brain are typical imaging patterns with CT or MRI, mostly affecting the parietal and occipital lobes (4). Involvement of frontal lobes, inferior temporal-occipital junction and cerebellum are described but less common (4). T2/FLAIR sequences are more sensitive than CT scan to detect PRES because of high sensitivity for subcortical and cortical edema which is the hallmark of PRES (5).

The exact pathophysiology is still unknown but the two most accepted theories are the vasogenic and

Tabel 1. — **Summary of the most known causes of PRES**

Hypertensive encephalopathy	
Eclampsia	
Immunosuppresive therapy	**cyclosporine**
	tacrolimus
Renal failure	
Acute intermittent porphyria	
Cytotoxic drugs	**oxaliplatine**
	5-fluorouracil
	opotecan
	paclitaxel
	gemcitabine
	bevacizumab
	sorafenib
	regorafenib
	sunitinib
	pazopanib
Sepsis	
Autoimmune disorders	**systemic lupus erythematosus**
	thrombotic thrombocytopenic purpura
	hypothyroidism
	cleroderma
	Crohn's disease
	ulcerative colitis
	primary sclerosing cholangitis
	rheumatoid artritis
	Sjögren syndrome
	polyarteritis nodosa
	granulomatosis with polyangiitis
	neuromyelitis optica

the cytotoxic theory. The vasogenic theory states that, when blood pressure rises above the autoregulatory capacity of the cerebral vasculature (with mean arterial pressure above 150-160 mmHg), this will lead to focal transudation of fluid and petechial hemorrhages due to a disruption of the endothelial junctions of the blood-brain barrier with a preference for the white matter (1,2,3). The cytotoxic theory states that a sudden, severe elevation of blood pressure can cause a vasospasm which leads to ischemia of brain tissue, cytotoxic edema and secondary extracellular edema (3). Neither theory covers the whole story since cases with normal blood pressure or lower blood pressure due to sepsis have been reported (3,6).

PRES in cases 1 and 2 was associated with mFOLFOX4. Oxaliplatin is a platinum derived drug that poorly penetrates the blood-brain barrier but, in combination with other leucotoxic agents, can cause endothelial injury and weakness of the cerebral endothelial wall through vasogenic edema (3). PRES in case 3 was associated with the use of regorafenib, an oral vascular endothelial growth factor (VEGF) multikinase inhibitor. A disruption of the VEGF pathway can cause a decrease in circulating nitric oxide which influences cerebral blood perfusion (2,7). VEGF is also an important factor for the permeability of cerebral vasculature and increased concentrations of circulating cytokines, which results in an increase adhesion of circulating leucocytes leading to increased vascular permeability. Both factors can cause interstitial brain edema (2). Thirdly, a known side effect of regorafenib and sunitinib is arterial hypertension, which also can induce PRES (7). In retrospect we noticed that the patient had remarkably higher blood pressures since she was treated with regorafenib in case 3. In analogy PRES has been regularly described in association with another VEGF inhibitor, bevacizumab and is considered a class effect (9).

The cases reported here of PRES in association with oxaliplatin and regorafenib are extremely rare and are one of the first cases described in the literature.

Due to lack of a specific treatment, supportive care as blood pressure control and convulsion treatment if present, is extremely important (2). The precipitating cause should be stopped or treated. In patients under anti-VEGF treatment, it might be important to anticipate treating arterial hypertension.

The prognosis of PRES is usually good and most of the patients make a recover complete within one or two weeks but sometimes up to several weeks, as mentioned in our cases (2,8). Even with early diagnosis and rapid intervention, there is a risk (although low) of persistent neurological symptoms in 10-20% of patients with PRES (2). Recurrence is rare if the cause is identified and if the blood pressure is well controlled.

The re-challenge of chemotherapy or oncological targeted therapy medication can be considered as long as close and constant monitoring of appropriate blood pressure levels is performed (8,9).

Our main goal is to increase awareness among physicians when a patient enters a hospital with (sub) acute encephalopathy and is treated with chemotherapy or oncological targeted therapy.

Conflict of interest

None.

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