International Journal of Cerebrovascular Disease and Stroke
Mabila AS et al. Int J Cerebrovasc Dis Stroke 6: 162.
www.doi.org/10.29011/2688-8734.000062
www.gavinpublishers.com

Case Report

PRES Secondary to the Lenvatinib-Pembrolizumab Combination in a Patient with Serous Endometrial Adenocarcinoma

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Citation: Salambo Mabila AS, Landais A, Accrombessi D, Nitcheu AW, Domingo R, et al. (2023) Pres Secondary to the Lenvatinib-Pembrolizumab Combination in a Patient with Serous Endometrial Adenocarcinoma. Int J Cerebrovasc Dis Stroke 6: 162. DOI: https://doi.org/10.29011/2688-8734.100162

Received Date: 04 September, 2023**; Accepted Date:** 08 September, 2023**; Published Date:** 11 September, 2023

Summary

The combination of Lenvatinib and Pembrolizumab has benefited from Early Access Authorization in France since March 2022 in the treatment of advanced or recurrent endometrialcancer.

We present a case of PRES secondary to the combination of Lenvatinib and Pembrolizumab inthe treatment of an invasive endometrial serous adenocarcinoma.

A 66-year-old woman with serous endometrial adenocarcinoma diagnosed two years earlier inthe context of peritoneal carcinomatosis, with dissociated response after 6 courses of CARBOPLATIN TAXOL, was put on second-line treatment with LENVATINIB and PEMBROLIZUMAB. The patient presented, five days after the third course, headaches of rapidly increasing intensity. Cerebral imaging was performed revealing T2 hypersignals, bilateral, subcortical, posterior, asymmetrical, and predominant on the right without ADC restriction, in favor of a PRES, motivating the discontinuation of the two incriminated molecules. The evolution was marked by the regression of clinical and radiological signs. The patient subsequently underwent a Pet scan, which revealed progressive disease with uterine, peritoneal, hepatic, adrenal, lymph node and pulmonary lesions, indicating the use of third-line CAELYX.

Our case highlights the importance of considering this new therapeutic combination (Lenvatiniband Pembrolizumab) as likely to be associated with PRES. Rigorous neurological clinical monitoring and the use of brain imaging in the face of signs suggestive of PRES are necessaryin patients benefiting from this treatment.

Keywords: PRES; Lenvatinib-Pembrolizumab combination; Endometrial adenocarcinoma

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a neurological disorder of (sub) acute onset characterized by varied neurological symptoms [1]. PRES is associated with a wide range of clinical presentations, including headache, focal neurological deficits, seizures, visual disturbances, and encephalopathy. The severity and acuity of clinical symptoms vary, although they usually occur with a rapid onset [2]. On average, approximately 40% of all patients diagnosed with PRES require intensive care monitoring and treatment due to serious complications such as status epilepticus, cerebral ischemia, intracerebral hemorrhage, or intracranial hypertension [1].

Several risk factors associated with PRES have been identified. PRES is associated with a multitude of diverse clinical entities, the most common of which are eclampsia, hypertension, and immunosuppressive therapy. Activation/disruption of the immune system has recently been considered a critical initial step in the pathogenesis of PRES and plays a central role in disease development [3,4]. Because PRES is reversible and easily treated by controlling blood pressure and stopping the offending immunosuppressive agent or decreasing the dose, it should be recognized quickly [4]. Immunosuppressive or cytotoxic drugs, such as Cyclosporin A, Tacrolimus/FK-506, Methotrexate, Sirolimus, Lenvatinib are implicated in the occurrence of PRES [3]. Some of these drugs are used in the management of endometrial cancer. In September 2019, the combination of Pembrolizumab (200 mg intravenously [IV] every 3 weeks) and Lenvatinib (20 mg orally [po] daily) received accelerated approval from the FDA for the treatment of cancer of advanced endometrium that had progressed on prior systemic therapy [5,6].

In France, the Early Access Authorization was granted on March 17, 2022 to the specialty LENVIMA (Lenvatinib) in the indication "in combination with Pembrolizumab, is indicated for the treatment of adult patients with cancer of the advanced or recurrent endometrium, whose disease progresses during or following previous platinum-based chemotherapy received at any stage and who are not eligible for curative surgery or radiotherapy" [7].

PRES is one of the various side effects of LENVATINIB known before the authorization of the combination. PEMBROLIZUMAB has been implicated in the occurrence of autoimmune encephalitis for several years [8]. There is evidence of a link between PRES and humanized monoclonal antibody monotherapy, after a single dose, with onset usually within weeks of treatment [9]. Here we report a case of advanced endometrial cancer with neurological manifestations of PRES caused by the combination of LENVATINIB and PEMBROLIZUMAB. The patient has given informed consent for the publication of this case report, including the images.

Case Presentation

66-year-old patient with serous endometrial adenocarcinoma diagnosed in March 2021 in the context of peritoneal carcinomatosis. She initially received chemotherapy with 4 courses of CARBOPLATIN TAXOL between April and June 2022. Two additional courses were recommended following a Multidisciplinary Gynecology-Oncology Consultation Meeting and were carried out between July and August 2022. A dissociated response was noted, motivating the switch to second-line treatment with LENVATINIB and PEMBROLIZUMAB. Three cures were carried out from November 18 to December 29, 2022. From January 3, 2023, the patient presented with rapidly increasing headaches.

A cerebral CT scan, then a cerebral MRI were performed, finding areas of edema of the subcortical parieto-occipital white matter, predominantly on the right side, with a mass effect, in T1 hypointensity, with hyperintensity in FLAIR and hyperintensity in diffusion-weighted (DWI) without restriction of apparent coefficient diffusion (ADC), in favor of a PRES.

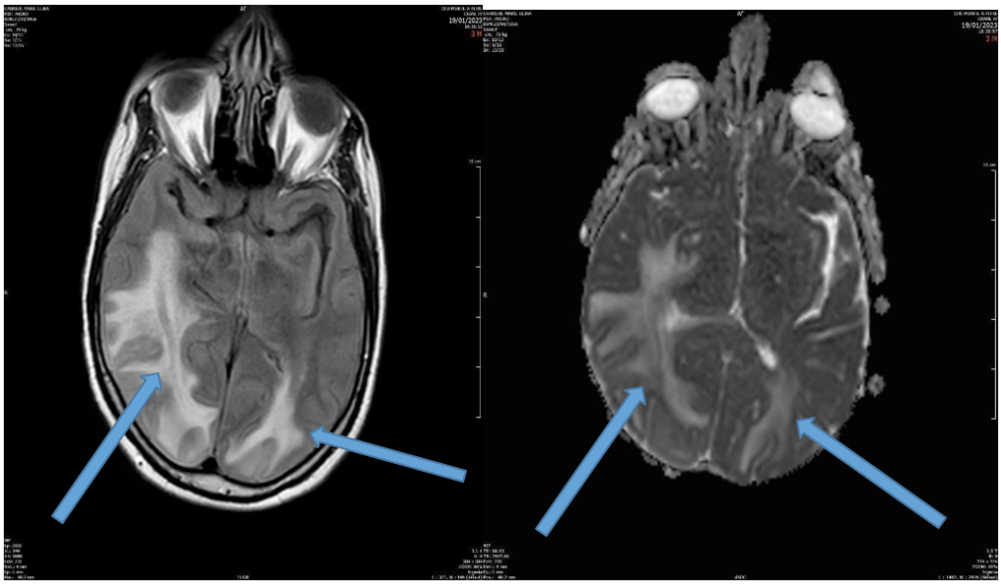

Figure 1: FLAIR and ADC from January 19, 2023.

She is transferred to the Neurology department. This was an awake patient, Glasgow 15, without neurological deficit, with a headache of 10/10 on the visual analogue scale. Blood work showed no significant alterations. Treatment with LENVATINIB and PEMBROLIZUMAB was stopped. It was noted a progressive regression of headaches with disappearance on the tenth day of hospitalization. Control cerebral MRIs were performed respectively on the seventh day after the onset of signs and two months later with regression of the lesions'extent.

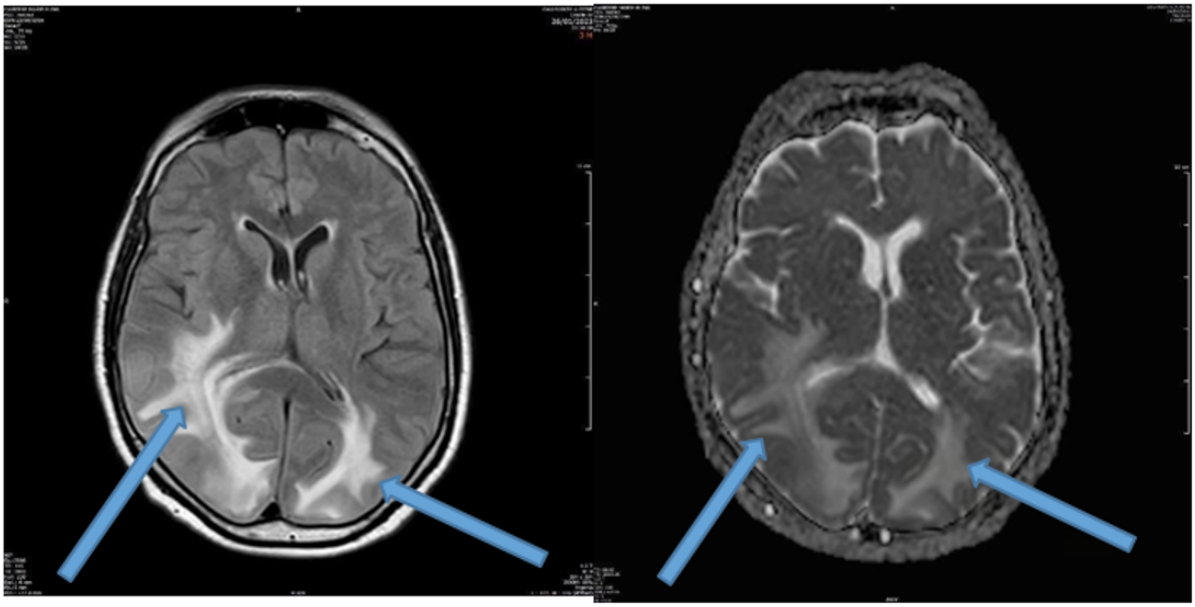

Figure 2: FLAIR and ADC from january 26, 2023.

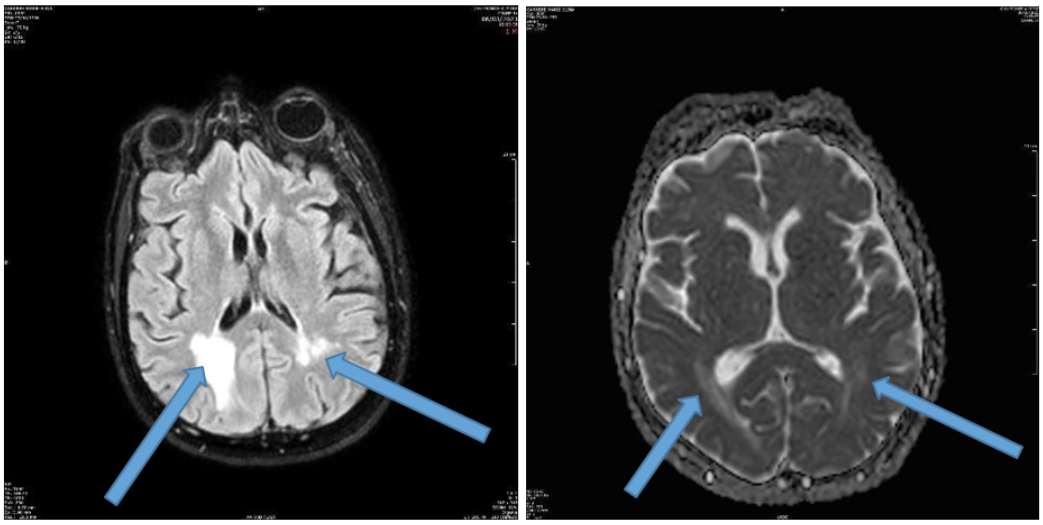

Figure 3: FLAIR and ADC from March 06, 2023.

From an extra-neurological point of view, a Pet scan carried out at the end of March revealed progressive disease with uterine, peritoneal, hepatic, adrenal, lymph node and pulmonary lesions, indicating the use of third-line treatment by CAELYX.

Discussion

Cancer patients can present neurological symptoms in several situations: paraneoplastic syndrome, neuro-infections in a context of dysimmunity favored by neoplasia and by the cancer treatment, cerebral metastases, cerebral infarctions in the prothrombotic state favoured by the cancer [8]. The diagnosis of PRES is not easy in this context and must be based on a particular etiological context (chemotherapy in our case), an evocative clinical picture which must motivate the request for imaging examinations [10]. The clinical presentation of PRES is polymorphic. The most common symptoms are epileptic seizures, impaired visual functions, headaches and altered psychological status [11]. The only symptom found in our patient was headache.

The headache associated with PRES is often of sudden onset, with or without associated neurological deficits or seizures. It is typically described as constant and dull, sometimes intractable, and has been reported in 50% of patients [2]. The syndrome has a myriad of imaging findings that are typical in many cases, but can also be confused with other entities [3].

The bilateral, subcortical, posterior, asymmetrical T2 hyperintensities, predominant on the right without ADC restriction found in our patient were very characteristic. The reversibility of lesions is one of the most important characteristics of PRES. However, this reversibility of the lesions, associated with the good prognosis of the patients, is inconstant. The increased ADC, witness of a vasogenic edema, is in favor of reversible lesions. Which happened in this case.

Moreover, no characteristic associated with the poor prognosis (brain stem involvement and signs of hemorrhage on the initial imaging) was found on the imaging of our patient [4]. The involvement of LENVATINIB in the occurrence of PRES has already been mentioned by some authors [8,9]. PEMBROLIZUMAB is more cited in the occurrence of autoimmune encephalitis [6,8].

Moreover, the only published case that we were able to consult of PRES occurring in a patient under the LENVATINIB and PEMBROLIZUMAB combination, attributed the etiology of this PRES exclusively to LENVATINIB, which was discontinued. Treatment was continued with PEMBROLIZUMAB alone, which proved to be ineffective on neoplasia and was later stopped [8].

Note, however, two cases found in the literature associating PEMBROLIZUMAB with PRES [9,12].

The limitation of this case report is related to the fact that the two drugs were initiated on the same day (in accordance with the protocol) and stopped at the same time after the diagnosis of PRES, making it difficult to establish the association of PRES with one or the other of the two molecules or both at the same time.

Conclusion

We presented a case of PRES diagnosed in a patient treated for invasive serous adenocarcinoma of the endometrium with the LENVATINIB-PEMBROLIZUMAB association. To our knowledge, this is the first case reported in France since the early access authorization granted to this association in March 2022. Given the declared efficacy of this drug combination

which could make its use more and more frequent, it is essential to raise awareness of these adverse effects both oncologists and neurologists.

Conflicts of Interest

The authors declare no conflict of interest.

Author Contributions

All authors contributed to the conduct of this work. All authors also declare that they have read and approved the final version of the manuscript.

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