Case Reports in Neurology

Case Rep Neurol 2022;14:149–156
DOI: 10.1159/000522308
Received: December 6, 2021
Accepted: January 22, 2022
Published online: March 15, 2022

Single Case – General Neurology

Cerebral Amyloid Angiopathy-Related Inflammation following Multiple Cancers and Chemotherapies

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Keywords
Cerebral amyloid angiopathy-related inflammation · Inflammatory cerebral amyloid angiopathy · Cancer · Chemotherapy

Abstract
Cerebral amyloid angiopathy-related inflammation (CAA-ri) is a rare autoimmune encephalopathy of aging caused by an autoantibody immune response against Aβ protein deposited in the brain of older adults affected by cerebral amyloid angiopathy (CAA) and Alzheimer's disease pathology. Its most common clinical manifestations are (sub)acute-onset cognitive and behavioral abnormalities, focal deficits, seizures, and headaches. Brain magnetic resonance imaging shows characteristic extensive and confluent white matter hyperintensities and CAA features. The response to immunosuppressive treatment is generally good. Here, we report the case of a 62-year-old patient with CAA-ri confirmed on biopsy, who had previously repeatedly received chemotherapy for multiple cancers. We summarize his clinical data, neuroradiological features, and therapeutic response and comment on the potential mechanisms connecting multiple cancers and chemotherapies with CAA-ri.

Introduction

Sporadic cerebral amyloid angiopathy (CAA) results from amyloid-β (Aβ) deposition in the wall of small- to medium-sized arteries, arterioles, and capillaries in the brain and leptomeninges [1]. It is a frequent cause of spontaneous lobar hemorrhages and dementia in the

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elderly [1]. Cerebral amyloid angiopathy-related inflammation (CAA-ri) is a rare autoimmune encephalopathy in which an inflammatory response occurs against Aβ deposit in CAA-affected vessels, causing headaches, focal neurologic deficits, rapid cognitive decline, and seizures [2]. Clinical and magnetic resonance imaging (MRI) criteria allow to approach a diagnosis of possible or probable CAA-ri, while definite diagnosis requires a brain biopsy [3]. High-dose corticosteroid therapy usually gives good clinical and radiological responses [2]. An increasing number of cases of CAA-ri are reported in the literature, but to the best of our knowledge, none of these cases is described in the context of multiple chemotherapies and cancers.

Case Report/Case Presentation

We report on the case of a 62-year-old male, right-handed patient. His medical history reveals a long-standing arterial hypertension, and esophagus and rectum cancers detected, respectively, in 2015 and 2018. Esophagus cancer was treated in 2015 by surgery, radiotherapy (45 Gy delivered in 25 fractions), and chemotherapy (carboplatin and paclitaxel). A relapse in 2017 was treated with radiotherapy (50.4 Gy in 28 fractions) and chemotherapy (5-fluorouracil and oxaliplatin). Rectum cancer was treated by radiotherapy (45 Gy in 25 fractions from October 2018 to November 2018), chemotherapy (5-fluorouracil and oxaliplatin from October 2018 to February 2019), and eventually surgery in May 2019. While considered in remission, he presented in October 2019 with headaches and two episodes of tonico-clonic seizures. Physical examination revealed a left hemiparesis, left hypoesthesia, left hemianopia, left hemineglect, apraxia, ataxia, and disorientation. His blood pressure was 160/90 mmHg. Brain computed tomography (CT) showed a right temporal and occipital hypodensity associated with edema and regional mass effect. On day 1, brain MRI showed large confluent white matter abnormalities in the right temporo-parieto-occipital region, compatible with vasogenic edema (hyperintensity in diffusion and fluid-attenuated inversion recovery [FLAIR] sequences with increased apparent diffusion coefficient), and petechial lesions (decreased signal in gradient echo sequence), as shown in Figure 1. The lesions were not enhanced after injection of gadolinium contrast agent (GCA) and were not suggestive of metastasis, lymphoma, or stroke. Electroencephalogram showed slow fronto-temporo-parietal rhythms, without paroxysmal activity. Because of a suspicion of endoluminal material in the right transverse sinus, anticoagulant treatment (low-molecular-weight heparin) was started in case of a central venous thrombosis. Levetiracetam was introduced as antiepileptic drug.

On day 5, motor deficit worsened although brain CT was unchanged. On day 7, the patient presented several tonico-clonic seizures. The electroencephalogram revealed a focal status epilepticus in the right parieto-occipital junction which required the addition of valproic acid and lacosamide. On day 12, MRI showed an increased number of petechial lesions and a progression of diffusion and FLAIR white matter hyperintensity (WMH) to the right thalamus (shown in Fig. 2), without enhancement after gadolinium contrast agent administration. The hypothesis of an atypical posterior reversible encephalopathy syndrome with multifocal hemorrhagic lesions was temporarily considered due to the history of chemotherapy and hypertension. Meanwhile, an exhaustive exploration had been obtained. The general and autoimmune biological assessments showed no anomaly. Serologies were negative for hepatitis B and C, HIV, CMV, EBV, varicella-zoster virus, herpes simplex virus, borrelia burgdorferi, syphilis, nocardia, histoplasma, and toxoplasma. Blood lymphocyte typing was normal. Cerebrospinal fluid (CSF) showed mild isolated hyperproteinorachia (533 mg/L, reference value [RV] 150–450 mg/L) with increased IgG (49 mg/L, RV 0–34 mg/L) and normal IgG index (0.7, RV <0.7), no oligoclonal bands and normal glucose levels (94 mg/dL, RV 60–100 mg/dL), and cell count (<200 red blood cells [RV <200], <5 nucleated cells [RV 0–5]). Total body PET-CT

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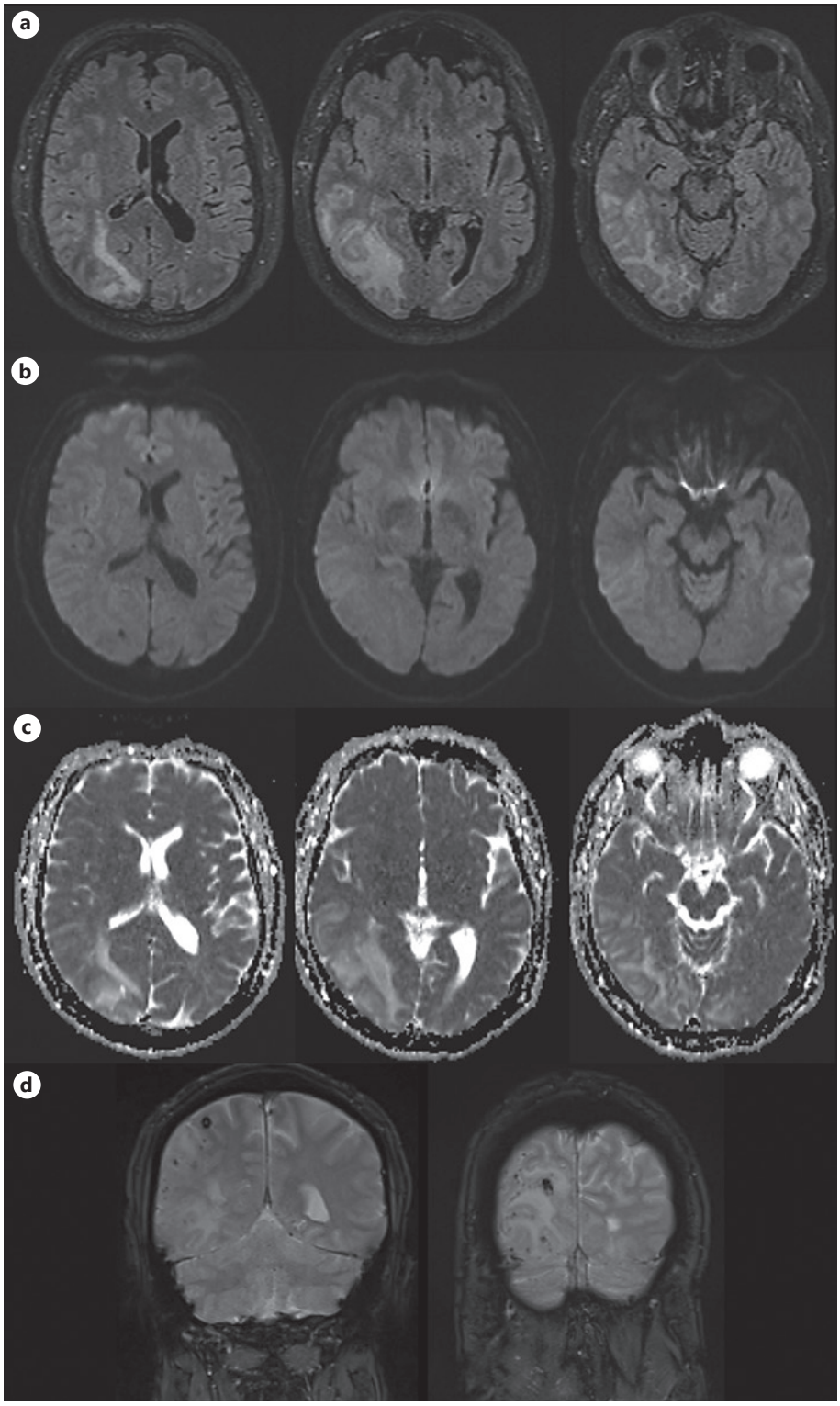

Fig. 1. First brain MRI (on day 1, 25 October 2019) showing a vast vasogenic edema in the right parieto-temporo-occipital region, and to a lesser degree the left occipital region, and several right parieto-temporo-occipital petechial lesions (confluent hyperintensities on FLAIR (**a**); no restriction of signal in diffusion (**b**); hyperintense signal on apparent diffusion coefficient (**c**); petechial lesions in gradient echo sequence (**d**)).

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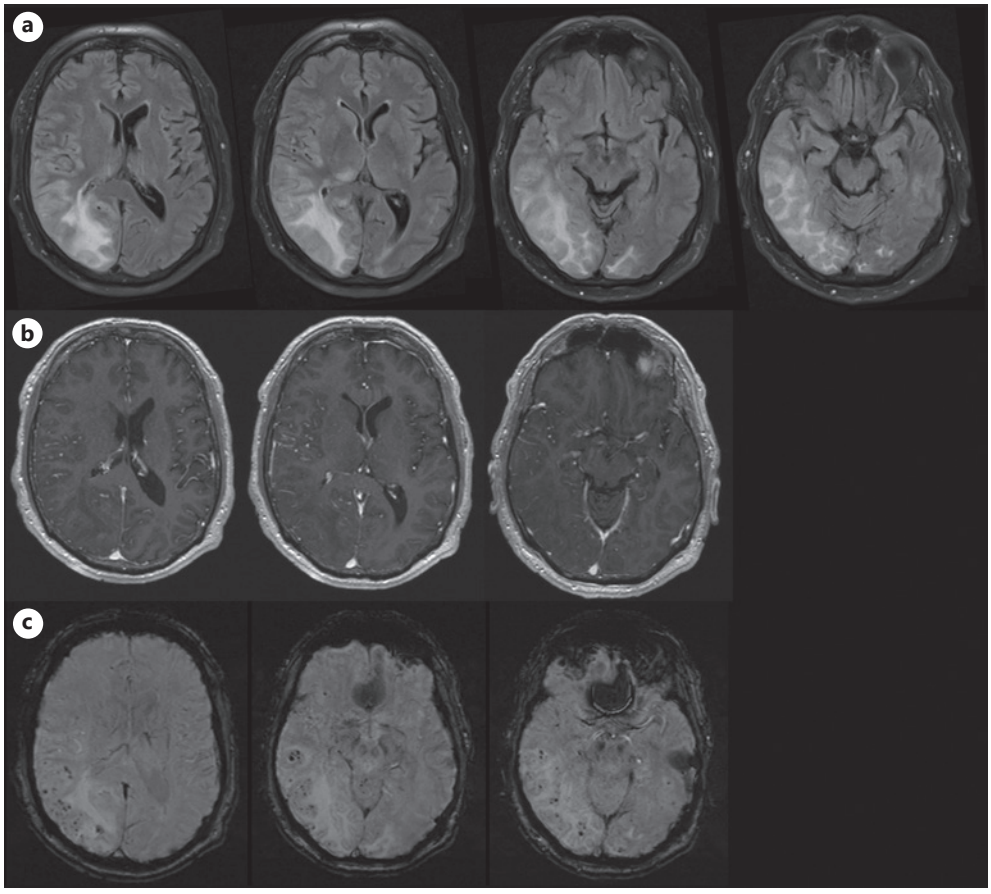

Fig. 2. Repeated MRI (on day 12, 5 November 2019) showing an increase in the right parieto-temporo-occipital hyperintensities, extending to the right thalamus (FLAIR with hyperintensities (**a**); T1 with gadolinium injection showing no enhancement (**b**); susceptibility weighted imaging showing multiple microbleeds (**c**)).

with FDG showed no suspect hypermetabolism. A cerebral biopsy was performed on day 34. Histopathology showed circumferential vascular Aβ deposits and multiple perivascular lymphocytes (shown in Fig. 3). The diagnosis of CAA-ri was made based on a proven CAA-positive vessel with perivascular lymphocytes, and the patient received intravenous methylprednisolone (1 g per day for 5 consecutive days), followed by oral therapy. On day 56, MRI showed a clear size regression of the right parieto-temporo-occipital FLAIR hyperintensity. The cognitive disorders improved although the left hemineglect, left hypoesthesia, and a left arm paresis persisted.

One year later, no recurrence of epilepsy had been observed. The patient described the persistence of anxiety attacks, and the clinical follow-up identified a persistent left hemianopia, left hemineglect, left hypoesthesia, and improving paresis and visuoconstructive disorders. MRI follow-up showed no CAA-ri recurrence episodes.

Discussion/Conclusion

The most common clinical syndrome encountered in CAA-ri is an acute or subacute encephalopathy with rapid cognitive decline, followed by seizure, headaches, and focal neurologic deficit [2]. Brain MRI shows asymmetric patchy or confluent T2 hyperintensities

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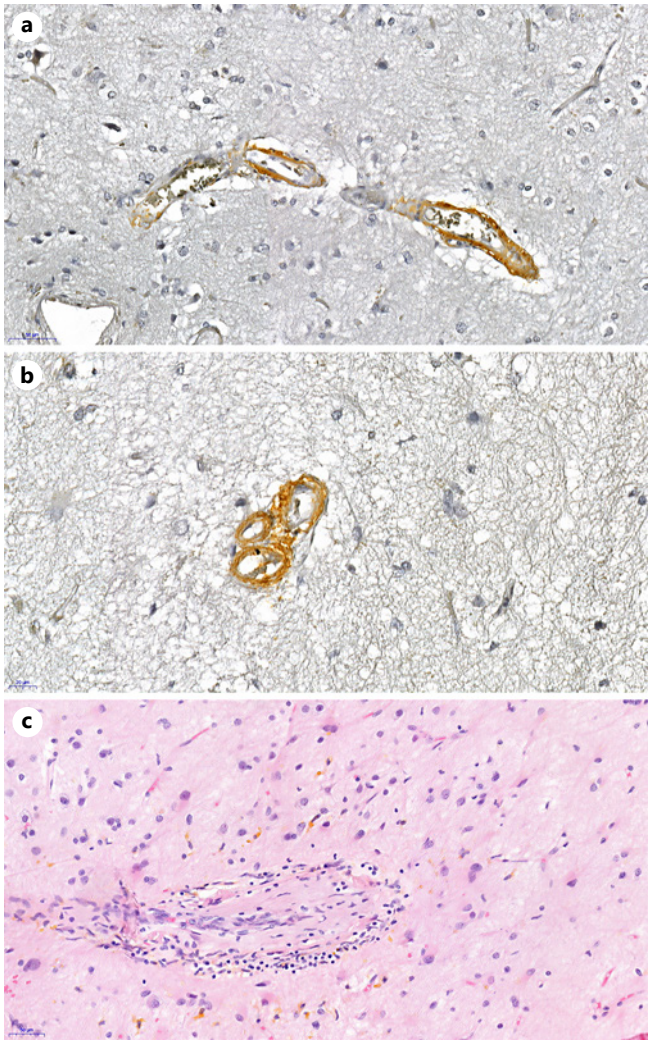

Fig. 3. Histopathology on brain biopsy. **a**, **b** Immunohistochemistry on paraffin sections with Anti-Beta Amyloid Monoclonal Antibody, Leica Biosystems, showing Aβ deposition within arterial wall (×300 magnification (**a**); ×400 magnification (**b**)). **c** Hematoxylin-eosin staining on paraffin sections, showing perivascular lymphocytes (×200 magnification).

extending to the immediate subcortical white matter and cortex, corresponding to vasogenic edema [2]. Definite diagnosis requires a brain biopsy [3]. Histopathology allows to distinguish two forms of CAA-ri: (1) inflammatory CAA, as observed in this patient, is defined by perivascular inflammation with lymphocytes and multinucleated giant cells surrounding Aβ-laden vessels, and (2) Aβ-related angiitis, defined by intramural or transmural inflammation, histiocyte and lymphocyte collections, possible granuloma formation, and a vasculitic destruction of the vessel wall [4]. To avoid the invasive risk of a brain biopsy, clinical and radiological criteria have been validated to approach a diagnosis of possible or probable CAA-ri, as shown in Table 1, with good sensitivity (82%) and specificity (97%) [3]. These criteria include an age >40 year, a typical clinical presentation, radiological evidence of underlying CAA, radiological evidence of vasogenic edema, and the exclusion of any other cause. MRI is the most sensitive diagnostic tool. CSF study may show inflammatory sign with lymphocytic pleocytosis (in 44% of cases) and elevated protein levels (in 83% of cases) [5]. During the acute phase of CAA-ri, anti-Aβ antibodies may be found in the CSF [6], suggesting a possible immune-mediated mechanism underlying the genesis of CAA-ri. Treatment strategy of CAA-ri relies on immunosuppression, usually by high-dosage intravenous corticosteroid treatment followed by oral administration

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Table 1. Criteria for the diagnosis of CAA-ri

Diagnosis	Criteria
Probable CAA-ri	Age ≥40 yr
	Presence of ≥1 of the following clinical features: headache, decrease in consciousness, behavioral change, or focal neurological signs and seizures; the presentation is not directly attributable to an acute ICH
	MRI shows unifocal or multifocal WMH lesions (corticosubcortical or deep) that are asymmetric and extend to the immediately subcortical white matter; the asymmetry is not due to past ICH
	Presence of ≥1 of the following corticosubcortical hemorrhagic lesions: cerebral macrobleed, cerebral microbleed, or cortical superficial siderosis
	Absence of neoplastic, infectious, or other cause
Possible CAA-ri	Age ≥40 yr
	Presence of ≥1 of the following clinical features: headache, decrease in consciousness, behavioral change, or focal neurological signs and seizures; the presentation is not directly attributable to an acute ICH
	MRI shows WMH lesions that extend to the immediately subcortical white matter
	Presence of ≥1 of the following corticosubcortical hemorrhagic lesions: cerebral macrobleed, cerebral microbleed, or cortical superficial siderosis
	Absence of neoplastic, infectious, or other cause

Auriel et al. [3].
ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; WMH, white matter hyperintensity.

tapered over several months [2]. Immunosuppressive treatment usually leads to clinical and radiological improvement in 72% of patients, but recurrences are described in 38.3% of patients within the following 24 months [2].

In our patient, the positive diagnosis of definite CAA-ri (inflammatory CAA subtype) is based on biopsy neuropathology, albeit it was already suggested by clinical and radiological findings as well as by the good clinical and radiological responses to corticosteroid therapy. Two synergistic components are believed to participate in the development of CAA-ri: vascular integrity and inflammation [7]. As for the former, Aβ, produced by neurons, is eliminated by phagocytosis and enzymatic degradation, or exits the brain via either perivascular drainage or the glymphatic system. Increased vascular permeability would expose extracellular Aβ to circulating pro-inflammatory mediators, facilitating the development of an anti-Aβ auto-immune response [8]. Both oxaliplatin and 5-FU lead to endothelial dysfunction, alter the blood-brain barrier, and can trigger posterior reversible encephalopathy syndrome [9]. Likewise, CAA-ri was reported during a treatment by bevacizumab, a monoclonal antibody targeting VEGF which jeopardizes vascular integrity [10].

The second key component of CAA-ri consists of an inflammatory reaction against amyloid. In this respect, a CAA-ri is understandable following anti-PD-1 immunotherapy [11], given that immune checkpoint inhibitors not only facilitate the therapeutic response against cancer cells but can also cause neuro-immune adverse events [12]. By contrast, a florid autoimmune reaction appears paradoxical in immunocompromised patients such as a patient receiving immunosuppressive therapy after heart transplantation [13] or, as in our case, a patient treated by iterative chemotherapies (the last one 8 months before onset of symptoms). In the latter case, one potential mechanism dwells in the homeostatic expansion by which immunocompetent cells repopulate the immune space and can skew it toward an effector memory type

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prone to inducing autoimmunity [14]. It can even be the case that the patient's immune system is genuinely defective, inducing both a tolerance to 3 cancers and untimely autoimmune responses, a situation observed in common variable immunodeficiency, for instance [15].

Conclusion

This original case of two neoplasms and chemotherapies followed by a biopsy-proven CAA-ri in a single patient raises the issue of the additive effects of vascular damage and skewed immune response in mounting a harmful response toward Aβ perivascular deposits.

Acknowledgment

We would like to thank Professor Steven M. Greenberg for giving us permission to use the information in Table 1.

Statement of Ethics

Ethical approval was not required for this study in accordance with local/national guidelines. Written informed consent for patient information and images to be published was provided by the patient.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no funding source for this article.

Author Contributions

Dr. Christophe Severijns has reviewed the literature about CAA-ri and searched for references on PubMed to build the discussion part. He has gathered the relevant information about the patient from the medical file and has written the manuscript and submitted it to Pr. Pierre Maquet for approval and correction. Dr. Emilie Drion managed the patient daily during the hospitalization. Dr.Elettra Bianchi provided a detailed histopathological analysis of the brain biopsy. Pr. Pierre Maquet has identified the case and provided a substantial bibliography about the subject. He supervised the directive line of the writing part and gave corrections to the final work.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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