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Iatrogenic Cerebral Amyloid Angiopathy–Related Inflammation

A Multicenter Case Series

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Abstract

Background and Objectives

Variants of cerebral amyloid angiopathy (CAA) have been increasingly reported. Iatrogenic CAA (iCAA) is a subtype arising in patients with a history of neurosurgery. Current etiopathogenetic hypotheses focus on previous exposure to contaminated materials, such as cadaveric dura, followed by a prion-like mechanism. CAA-related inflammation (CAA-ri) represents the inflammatory variant of CAA, usually with a good response to immunosuppressive therapy. To date, the association between iCAA and CAA-ri has not been clarified yet. This study reports cases of iCAA evolving into CAA-ri, emphasizing the clinical and radiologic overlaps between these conditions.

Methods

This retrospective observational study included patients with clinical and radiologic features of CAA-ri and a history of neurosurgical intervention, observed at 2 Italian neurologic centers. Patients were identified from CAA databases and screened for neurosurgical history before 1990. Eligible cases met diagnostic criteria for CAA-ri. Clinical data were anonymized and included surgical details, evidence of amyloid-β in the CNS (amyloid-PET, CSF biomarkers, genetic screening), and CAA-ri features (symptoms, imaging findings, treatment, and outcomes).

Results

We identified 6 patients with iCAA who developed clinical and instrumental features of CAA-ri during their follow-up. The mean age at neurosurgery was 17.2 years (range: <1–43) while the onset of CAA-ri occurred at 61.8 years (range: 48–79), with an average latency of 44.7 years (range: 36–59). Despite immunosuppressive treatment, 2 patients experienced a rapid decline in their clinical condition and deceased within a few months from CAA-ri onset.

Discussion

This study increases awareness about the potential occurrence of CAA-ri in patients with iCAA, confirming its aggressive nature and highlighting the importance of neuroinflammation in the pathogenesis of the disease. In these patients, CAA-ri seems to be associated with a severe clinical course and a poor response to steroid treatment, often resulting in a fatal outcome in the short term.

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Glossary

Aβ = amyloid-β; **CAA** = cerebral amyloid angiopathy; **CAA-ri** = CAA-related inflammation; **CMB** = cerebral microbleed; **cSS** = cortical superficial siderosis; **FLAIR** = fluid-attenuated inversion recovery; **iCAA** = iatrogenic CAA; **ICH** = intracerebral hemorrhage; **LPD** = lateralized periodic discharge; **SAH** = subarachnoid hemorrhage; **SWI** = susceptibility-weighted imaging; **WMHs** = white matter hyperintensities.

Introduction

Cerebral amyloid angiopathy (CAA) is a major cause of spontaneous cerebral bleeding in the elderly population.[1] The disease is caused by the deposition of amyloid-β (Aβ) in cortical and leptomeningeal vessels of the brain.[2]

The latest revision of the diagnostic Boston criteria (version 2.0) considers both clinical and MRI findings, along with pathologic confirmation when available.[3] Clinical features include spontaneous lobar intracerebral hemorrhage (ICH), transient focal neurologic episodes, and cognitive impairment or dementia. Neuroradiologic features include cerebral microbleeds (CMBs), cortical superficial siderosis (cSS), subarachnoid hemorrhage (SAH), multispot white matter hyperintensities (WMHs), and enlarged perivascular spaces in the centrum semiovale (CSO-PVS).

Along with the more common sporadic form of the disease (sCAA), in the past few years, rare cases with an iatrogenic cause have emerged, often linked to past neurosurgical interventions, usually before the 1990s.[4] Although not yet definitively confirmed, the causes of iatrogenic CAA (iCAA) seem to involve the direct transmission of the Aβ protein through contaminated material, particularly cadaveric lyophilized dura, followed by a prion-like mechanism that may also involve neuroinflammatory processes.[5] The suspicion of iCAA arises with the early onset of neurologic symptoms, typically before age 50. However, cases with a later onset, similar to sCAA, have also been reported.[6,7]

According to the proposed, but not yet validated, diagnostic criteria for iCAA (also termed "Queen Square criteria"), patients presenting with clinical and radiologic characteristics consistent with CAA and a history of neurosurgical intervention, particularly involving exposure to contaminated material such as cadaveric human CNS tissues (brain, meninges, and pituitary-derived hormones), can be classified as having "possible" iCAA. Further analyses confirming the accumulation of Aβ in the CNS, along with the exclusion of a genetic cause, support a diagnosis of "probable" iCAA.[8]

CAA-related inflammation (CAA-ri) is the inflammatory variant of CAA.[9] This acute or subacute encephalopathy is characterized by highly variable features depending on the area of the brain affected. Symptoms may include behavioral changes, cognitive impairment, headache, seizures or epilepsy, and focal neurologic deficits.[10,11] In addition to the radiologic features typical of CAA, CAA-ri is also characterized by asymmetric confluent white matter edema, with inflammatory lesions involving leptomeninges and cortical and subcortical brain structures.[12-14] It is important to promptly recognize this condition, because patients generally respond well to immunosuppressive treatment, typically with high doses of IV steroids.[15-17] Moreover, they should undergo a close follow-up because inflammatory relapse may occur even many years after the onset.[18] Although considered a rare condition,[14,19] radiographic features of CAA-ri were recently observed in approximately 20% of patients with CAA.[20]

Because iCAA has only recently been described in the literature, its clinical and radiologic characteristics have not yet been fully elucidated. In particular, iCAA and CAA-ri have been recently described only in a single patient.[21] In this study, we report a case series of individuals diagnosed with iCAA who, during their clinical and radiologic follow-up, developed CAA-ri.

Methods

eMethods are reported as Supplementary material.

Standard Protocol Approvals, Registrations, and Patient Consents

This study received ethical approval from the institutional review boards of the Fondazione IRCCS Istituto Neurologico Carlo Besta of Milan and the Fondazione IRCCS San Gerardo dei Tintori of Monza, Italy. Written informed consent was obtained from all patients (or guardians of participants). Research was performed following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines.[6]

Data Availability

Anonymized data not published within this article will be made available on reasonable request from any qualified investigator.

Results

Study Population

In a retrospective review of 433 CAA cases observed at the study centers,[22] 38 were classified as iCAA, of whom we identified 6 patients (3 women) with iCAA who developed CAA-ri during their follow-up (15.8%). According to the Queen Square diagnostic criteria,[8] 3 patients (cases I, II, and IV) were diagnosed with "possible" iCAA and 3 (cases III, V,

and VI) with "probable" iCAA. eTable 1 lists the characteristics of patients with iCAA while eTable 2 summarizes the clinical, instrumental, and pharmacologic features of CAA-ri. Some of the patients described herein (cases III and V) were previously reported in other case series.[7,23]

The mean age at neurosurgery was 17.2 years (SD 16.2 years), ranging from <1 to 43 years. The mean age at CAA-ri onset was 61.8 years (SD 11.1 years), ranging from 48 to 79 years. The mean interval between the neurosurgical intervention and the diagnosis of CAA-ri was 44.7 years (SD 8.7 years), ranging from 36 to 59 years. None of the patients reported a family history of brain hemorrhage or cognitive impairment.

Case Descriptions

A case-by-case description of patients included in the study is provided further.

Case 1

In the late 1980s, at the age of 43, this woman underwent a neurosurgical procedure of craniocervical decompression with apposition of Lyodura, because of Chiari malformation type 1, as confirmed by medical documentation. The surgery was well tolerated, without any neurologic sequelae.

She came to our attention at the age of 79 with the onset of frequent focal seizures, characterized by partial loss of contact, left-sided head rotation, and mouth clonus. On admission, neurologic examination revealed left hemiparesis with fluctuations of consciousness. Head CT scan demonstrated diffuse hypodensity of the white matter, without acute lesions (Figure 1A). EEG showed right temporal focal *status epilepticus* (eFigure 1A) while lumbar puncture results were normal, including virologic investigations and the titer of major antibodies responsible for autoimmune encephalitis.

The patient was treated with IV infusion of diazepam 10 mg, followed by levetiracetam 3,000 mg daily; however, frequent seizures persisted. MRI performed 2 days after symptom onset showed, on fluid-attenuated inversion recovery (FLAIR) sequence, a hyperintense lesion involving the right frontoinsular cortex, uncus, and hippocampus (Figure 1A); extensive cSS in both frontal and left parietal lobes on susceptibility-weighted imaging (SWI); diffused vascular damage of the white matter (Fazekas score 3); and 2 small acute hemorrhagic lesions in the right temporal and left frontal lobes (Figure 1B). Overall, the clinical and instrumental findings were consistent with "probable" CAA-ri.

The patient started treatment with IV methylprednisolone 1 gr/daily for 5 days, followed by oral prednisone 1 mg/kg/daily, reporting rapid and significant improvement. In particular, seizures gradually resolved and alertness returned to normal. EEG showed resolution of lateralized epileptiform activity (eFigure 1B). A follow-up brain MRI scan 2 weeks after immunosuppressive therapy revealed the regression of the inflammatory lesions in the right hemisphere (Figure 1C). One month later, the patient was admitted to another hospital because of a bacterial urinary tract infection and prednisone was discontinued. During hospitalization, epilepsy relapsed with frequent seizures that were resistant to several antiseizure medications (ASMs), including phenobarbital, valproate, and clonazepam. Brain MRI showed gliotic outcomes from the previous lesion, with *ex vacuo* enlargement of the right temporal horn and thinning of the adjacent parenchyma (Figure 1D). Owing to suspicion of cerebral inflammatory reactivation (CAA-ri recurrence), the patient was treated with IV methylprednisolone 1 gr/daily for 4 days, but without any clinical improvement. Her clinical conditions rapidly worsened, and the patient died 5 months after symptom onset.

Case 2

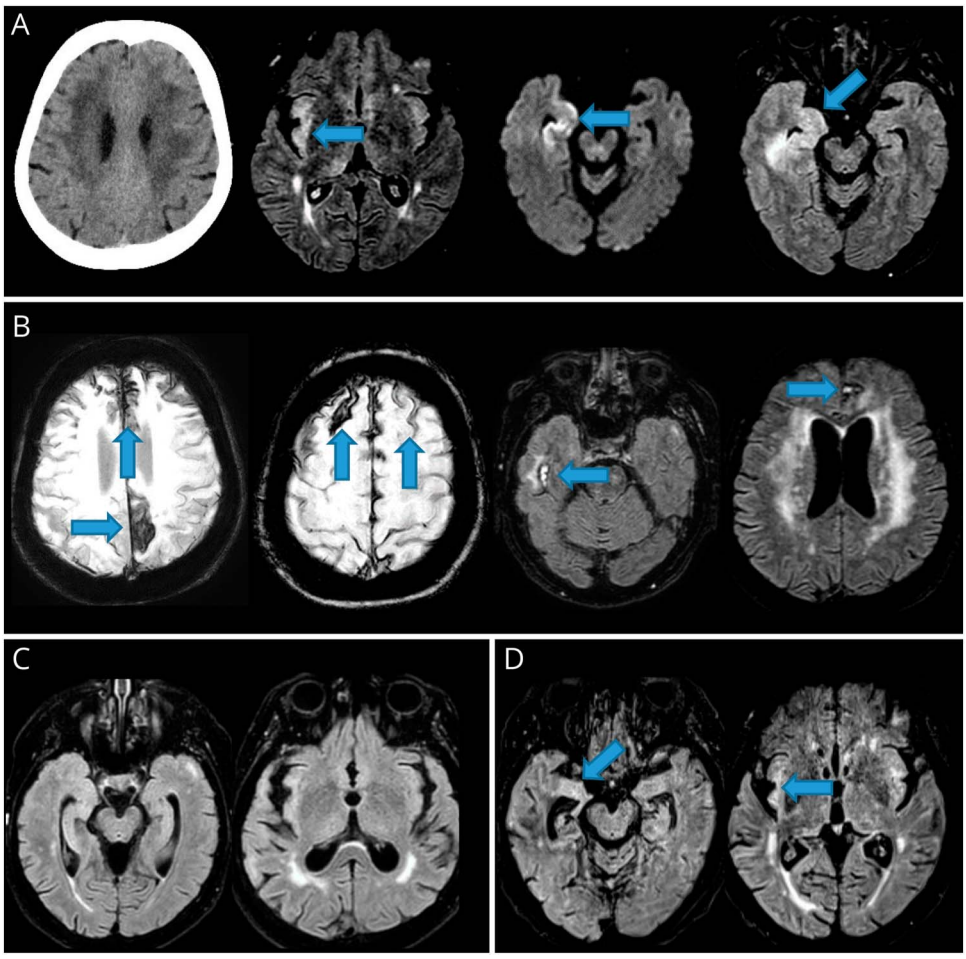
In the early 1980s, at the age of 24, this woman underwent neurosurgery for the removal of a large right frontal meningioma, with subsequent repositioning of the bone operculum, application of *dura mater*, and placement of several metal clips on the arteries of the circle of Willis, as confirmed by medical documentation. The intervention was well tolerated and left no neurologic deficit.

At the age of 64, she developed acute left hemiparesis involving both limbs, together with ipsilateral focal seizures. Head CT scan showed a right temporal ICH (Figure 2A, left panel). Digital subtraction angiography did not reveal any vascular malformation provoking the hemorrhagic lesion. The patient was started on ASM treatment with levetiracetam 500 mg twice daily with resolution of seizures. A follow-up head CT scan 1 month later showed complete resolution of the ICH (data not shown), and neurologic examination confirmed stable mild left hemiparesis. Brain MRI was not performed at that time.

After 3 years of clinical stability, at the age of 67 years, the patient returned to our attention with headache and dysarthria. On admission, neurologic examination revealed left hemiparesis and floating consciousness. Head CT scan revealed a right parietal cortical-subcortical digitated hypodense lesion, without bleeding (Figure 2A, right panel); angio-CT sequence excluded acute thrombosis. EEG showed subcontinuous interictal epileptiform activity in the right parietal derivations (eFigure 2A). The patient was treated with IV acute infusion of diazepam 20 mg, followed by levetiracetam 1,000 mg twice daily and lacosamide 150 mg twice daily, which significantly reduced epileptiform activity on follow-up EEG (eFigure 2B). However, clinical status remained unchanged, with persistence of lateralized hemisyndrome and speech difficulties.

Brain MRI performed 1 week later confirmed the presence of an extensive edematous lesion, associated with a recent hemorrhage in the right parietal lobe. A SWI sequence showed bilateral cSS and CMBs in the left posterior and right anterior temporal lobes (Figure 2B). Clinical and

Figure 1 Neuroradiologic Features of Case 1



Head CT scan showing diffuse hypodensity of the white matter, without acute lesions (left). Brain MRI performed 2 days after the onset of neurologic symptoms and before steroid treatment, showing on FLAIR sequence, a hyperintense lesion involving the right frontoinsular cortex, uncus, and hippocampus (A). Extensive cSS at both frontal and left parietal lobes (SWI sequence); diffuse vascular damage of the white matter (Fazekas score 3); and 2 small acute hemorrhagic lesions in the right temporal and left frontal lobes (FLAIR sequence) (B). Follow-up brain MRI after steroid treatment showing the regression of inflammatory lesions in the right temporal lobe and frontoinsular cortex (FLAIR sequence, C). Brain MRI performed during the second hospitalization showing gliotic sequelae of the previous alteration, with *ex vacuo* enlargement of the right temporal horn and thinning of the adjacent parenchyma (FLAIR sequence, D). Arrows indicate the main radiologic characteristics. cSS = cortical superficial siderosis; FLAIR = fluid-attenuated inversion recovery; SWI = susceptibility-weighted imaging.

instrumental data were consistent with "probable" CAA-ri. The patient was treated with IV methylprednisolone 1 gr/daily for 5 days, followed by IV dexamethasone 8 mg/daily, but without any significant clinical improvement.

One week later, the patient became acutely comatose state. Head CT scan revealed 2 new lobar hemorrhagic lesions, one in the left temporal lobe and the other localized in the right frontal lobe (Figure 2C). Owing to significant mass effect, the right frontal ICH was surgically evacuated; however, the patient remained comatose. A follow-up brain MRI scan confirmed diffuse asynchronous hemorrhagic lesions at different stages of evolution (Figure 2D). Her clinical conditions rapidly deteriorated, and the patient died 6 weeks after the onset of CAA-ri.

Case 3

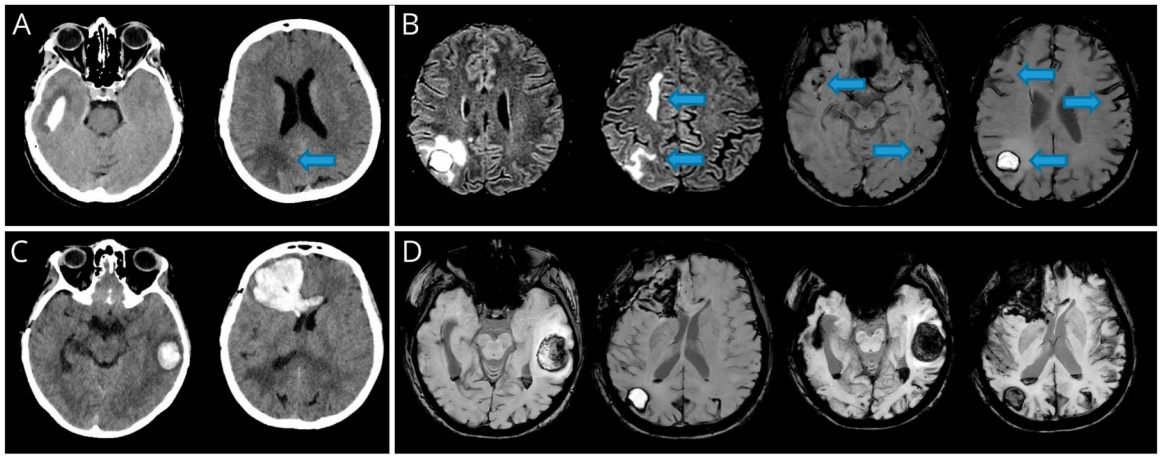
In the early 1980s, at the age of 8, this male patient underwent neurosurgery for the evacuation of a left frontal post-traumatic extradural hematoma. The intervention included a dural graft with material not specified. The patient reported no neurologic sequelae.

At the age of 45, he presented transient episodes of paresthesias of the right upper limb, suggestive of focal seizures. On admission, neurologic examination was normal. Brain MRI showed widespread hyperintense alterations of the bilateral white matter (Fazekas score 3), with bilateral CSO-PVS (Figure 3A); a T2*-weighted sequence revealed diffuse cSS and CMBs (Figure 3B). Data were consistent with "probable" CAA. The patient was started on ASM with lamotrigine 125 mg twice daily, achieving complete seizure control.

To better characterize this early-onset CAA case, lumbar puncture was performed and it revealed reduced Aβ-42 (321, normal value >640 pg/mL), with increased TAU and p-TAU (TAU 769 pg/mL, normal value <450 pg/mL; p-TAU 113, normal value <61 pg/mL). Amyloid-PET with flutemetamol showed diffuse cortical uptake of the tracer; genetic screening for *APP*, *PSEN1*, *PSEN2*, and *TTR* was negative, and the *APOE* genotype was ε3/3.

Three years later, at the age of 48, the patient presented with episodes of paresthesias involving the left side of the face. On

Figure 2 Neuroradiologic Features of Case 2

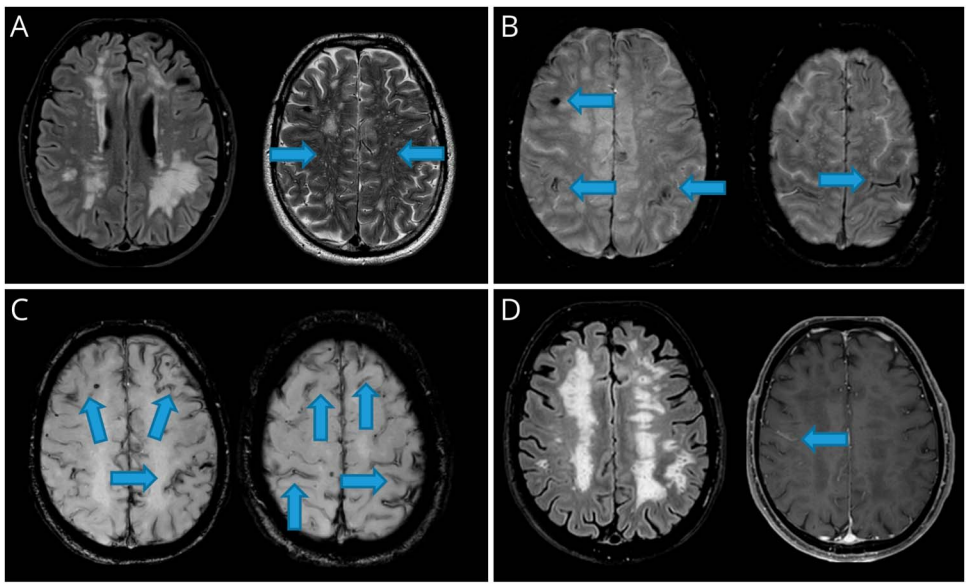


Head CT scan at age 64 showing right temporal ICH (left panel). Head CT scan 3 years later showing a right parietal cortical-subcortical digitated hypodense lesion, without bleeding (right panel, A). Brain MRI assessed 1 week later and before steroid treatment showing (from left to right) extensive edema, associated with a recent hemorrhagic lesion in the right parietal lobe (FLAIR sequence), along with bilateral cSS and left posterior and right anterior temporal CMBs (SWI sequence) (B). Head CT scan after an acute comatose state showing a new ICH in the left temporal lobe (left panel) and a larger ICH in the right frontal lobe with significant mass effect (right panel, C). Follow-up brain MRI after surgical evacuation of the right frontal ICH showing diffuse, asynchronous hemorrhagic lesions at different stages of evolution in both hemispheres (SWI sequence) (D). Arrows indicate the main radiologic characteristics. CMBs = cerebral microbleeds; cSS = cortical superficial siderosis; FLAIR = fluid-attenuated inversion recovery; ICH = intracerebral hemorrhage; SWI = susceptibility-weighted imaging.

admission, neurologic examination was normal. Head CT scan was negative for acute lesions, and angio-CT scan excluded arterial thrombosis. Brain MRI reported a moderate increase in the hemorrhagic load compared with the previous scan, including both CMBs and disseminated cSS (Figure 3C). There was also progression of bilateral WMH damage, and a subtle hyperintense lesion with contrast enhancement was observed in the right frontal sulcus, suggestive of inflammation (Figure 3D).

Clinical and radiologic data were consistent with "possible" CAA-ri. The patient was treated with oral prednisone 1 mg/kg/d for 2 weeks, tapered and discontinued over 2 months. During steroid treatment, the patient reported complete resolution of the transient neurologic episodes. A follow-up brain MRI scan assessed 2 weeks later did not detect contrast enhancement in the right frontal region (data not shown). At the last follow-up 1 year later, the patient remained asymptomatic with normal neurologic examination.

Figure 3 Neuroradiologic Features of Case 3



Brain MRI at age 45 showing diffuse hyperintense alterations of the bilateral white matter (left panel) and bilateral CSO-PVS (right panel, A); T2*-weighted sequence revealing diffuse cSS and CMBs (B). Follow-up brain MRI 3 years later showing, on the SWI sequence, an increase in the hemorrhagic load with spread of multiple hemosiderin deposits, including both CMBs and disseminated cSS (C). FLAIR sequence demonstrating diffuse white matter vascular damage (left panel) and T1 sequence with contrast enhancement (right panel) revealing a subtle hyperintense lesion in the right frontal sulcus with contrast enhancement, suggestive of inflammation (D). Arrows indicate the main radiologic characteristics. CMBs = cerebral microbleeds; cSS = cortical superficial siderosis; FLAIR = fluid-attenuated inversion recovery; SWI = susceptibility-weighted imaging.

Case 4

In the late 1950s, at the age of 3, this male patient underwent neurosurgery for a post-traumatic dural arteriovenous fistula, which was complicated by a bacterial infection treated with antibiotics. After surgery, the patient developed focal epilepsy, which was well controlled with carbamazepine 600 mg twice daily. We were unable to retrieve further details regarding the possible use of human-derived material.

At the age of 60, the patient presented with a cluster of focal motor seizures involving the left limbs, evolving into bilateral tonic-clonic seizures. Brain MRI showed diffuse ischemic vascular damage in the white matter (Fazekas score 3), a small right frontoparietal ICH, and bilateral cSS and CMBs. The findings were indicative of "probable" CAA (Figure 4A). Angio-CT scan excluded any vascular abnormalities responsible for the hemorrhagic lesions.

Over the following 2 years, the patient reported a gradual decline in cognitive functions, especially with memory, attention, and concentration. At the age of 62, the patient's conditions further worsened. On hospital admission, neurologic examination was characterized by mild left ataxic hemiparesis, extrapyramidal signs, and psychomotor agitation. A follow-up brain MRI scan confirmed severe diffuse vascular damage, along with hyperintense edematous lesions and gadolinium contrast enhancement in the right hemisphere (Figure 4B). Clinical and radiologic data were compatible with "probable" CAA-ri. The patient was treated with IV methylprednisolone 500 mg daily for 5 days. However, there was no significant change in neurologic status. A follow-up brain MRI scan 1 month later showed persistence of the inflammatory lesions in the right hemisphere, with moderately increased contrast enhancement (Figure 4C).

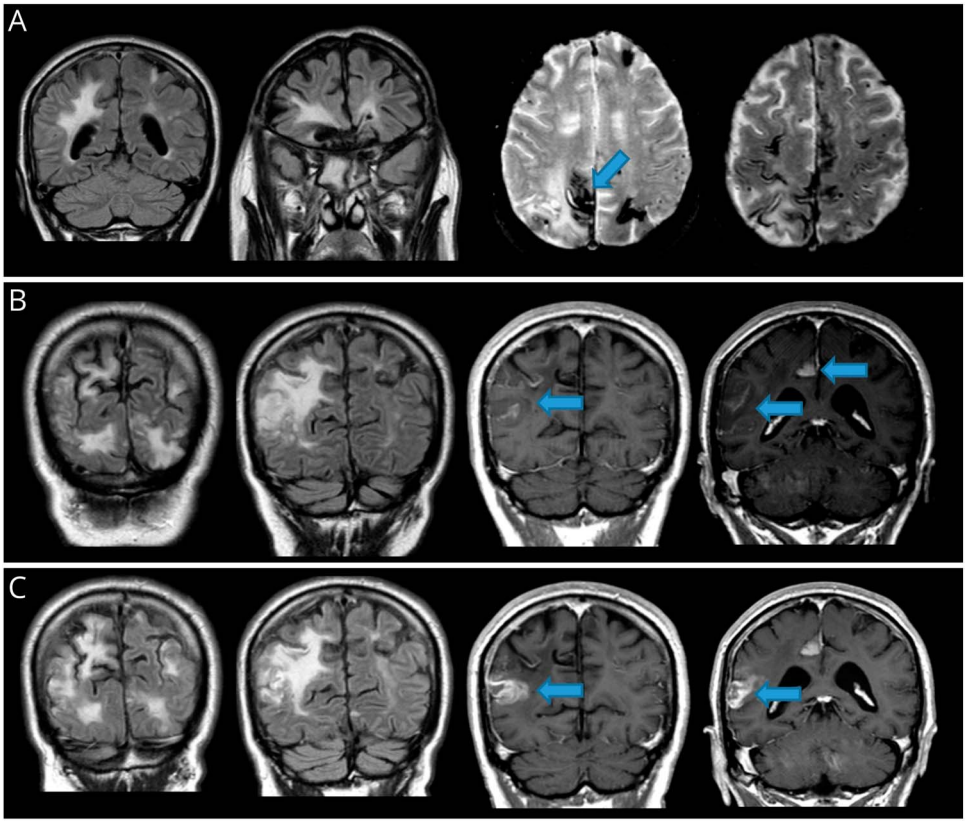
In the following months, the patient's clinical conditions progressively worsened, leaving him totally dependent for daily activities and requiring constant supervision by caregivers. He was eventually lost to follow-up and died at 66 years.

Case 5

In the early 1970s, at the age of 10 months, this female patient underwent neurosurgery for the treatment of a cervical dermal sinus, with application of Lyodura. The intervention was well tolerated without clinical consequences.

At the age of 46, the patient was admitted to another hospital for the onset of focal seizures, characterized by transient vertigo, speech difficulties, and paresthesias affecting the right limbs and face. Head CT scan with angio-CT sequence was negative; lumbar puncture revealed normal parameters and

Figure 4 Neuroradiologic Features of Case 4

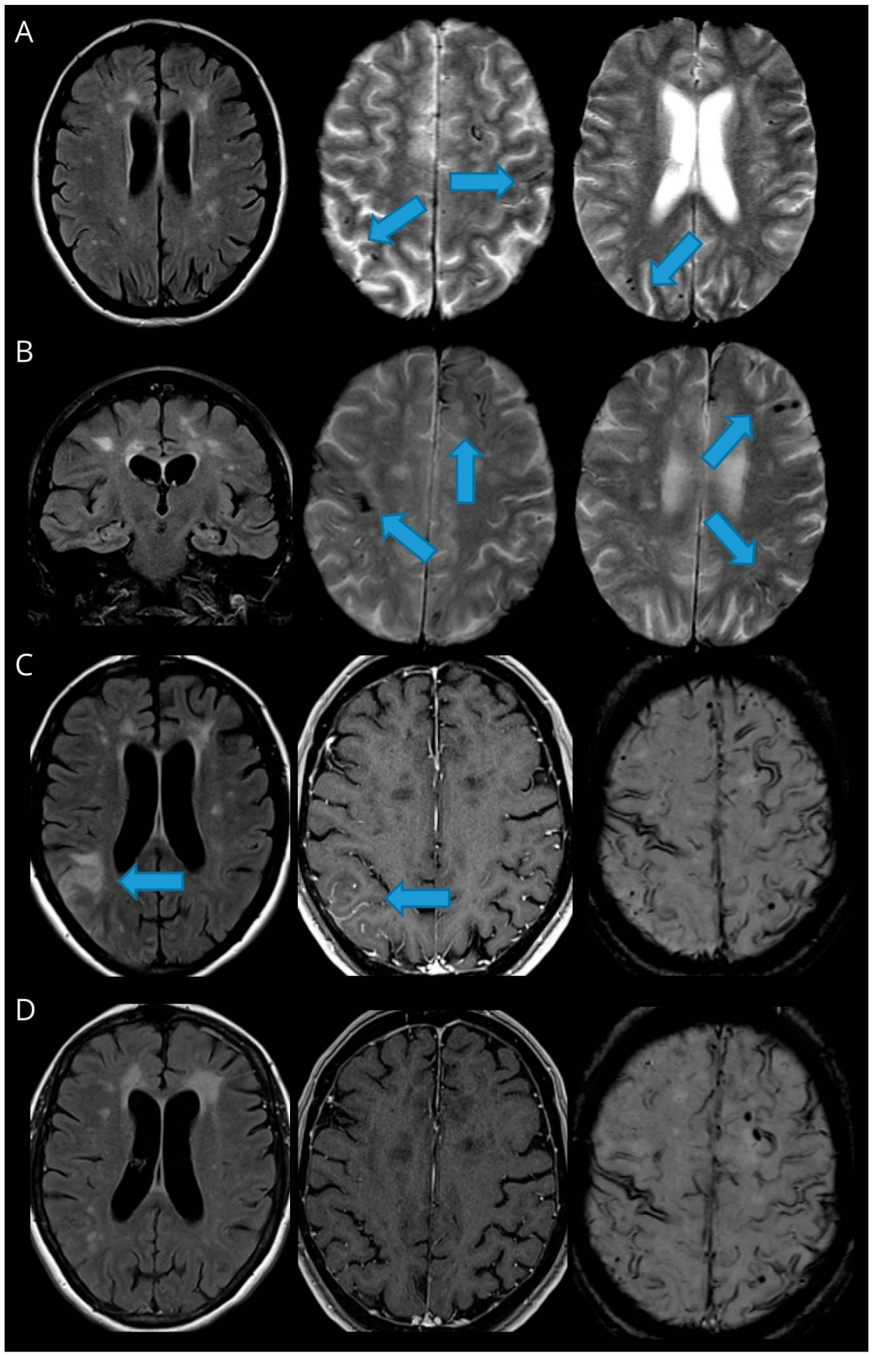


Brain MRI at age 60, showing diffuse ischemic vascular damage involving the white matter (Fazekas score 3, FLAIR sequence), with a small right frontoparietal ICH and bilateral cSS and CMBs (SWI sequence), indicative of "probable" CAA (A). Brain MRI 2 years later revealing edema on FLAIR sequence, with T1 gadolinium contrast enhancement, involving the right hemisphere, indicative of "probable" CAA-ri (B). Follow-up brain MRI after steroid treatment reporting the persistence of inflammatory lesions (FLAIR sequence), with moderately increased contrast enhancement (C). Arrows indicate the main radiologic characteristics. CMBs = cerebral microbleeds; cSS = cortical superficial siderosis; FLAIR = fluid-attenuated inversion recovery; ICH = intracerebral hemorrhage; SWI = susceptibility-weighted imaging.

excluded infectious causes. EEG showed left temporal epileptiform abnormalities (data not shown). Brain MRI reported multiple small ischemic lesions in both hemispheres, a few CMBs in the right occipital lobe, and cSS involving the left central sulcus (Figure 5A). The patient was started on ASM with carbamazepine 200 mg twice daily, achieving complete seizure control, and received antiplatelet treatment with acetylsalicylic acid 100 mg daily. Owing to the absence of further seizures, carbamazepine was discontinued 2 months later while the antiplatelet therapy was maintained.

At the age of 49, the patient was readmitted to the same hospital for recurrent episodes of hypoesthesia in the left perioral region, extending to the ipsilateral arm, which resolved spontaneously within few minutes. Brain MRI revealed a moderate increase in diffuse vascular damage of the bilateral white matter (Fazekas score 3), along with a small right frontal subacute ICH and augmented hemorrhagic lesions, including left frontal anterior and right posterior cSS and a few left frontal CMBs on T2*-weighted sequence (Figure 5B). Digital subtraction angiography was negative. The overall clinical and

Figure 5 Neuroradiologic Features of Case 5



Brain MRI at age 46 showing multiple small ischemic lesions in both hemispheres (FLAIR sequence), a few CMBs in the right parieto-occipital region, and subtle cSS (T2*-weighted sequence) involving the left central sulcus (A). Brain MRI 3 years later revealing progression of bilateral white matter diffuse vascular damage (FLAIR sequence) and increased hemorrhagic lesions, including left frontal anterior and right posterior cSS and a few left frontal CMBs on the T2*-weighted sequence (B). Brain MRI assessed during CAA-ri, before steroid treatment, showing an inflammatory lesion in the right inferior parietal region (FLAIR sequence), with gadolinium contrast enhancement, together with increased CMBs in both hemispheres and cSS (SWI sequence) in bilateral frontal and parietal lobes (C). Follow-up brain MRI assessed after steroid treatment showing regression of the inflammatory lesion (FLAIR sequence) with resolution of the previous contrast enhancement and no significant variation of the hemorrhagic load (SWI sequence) (D). CMBs = cerebral microbleeds; cSS = cortical superficial siderosis; FLAIR = fluid-attenuated inversion recovery; SWI = susceptibility-weighted imaging.

instrumental findings were consistent with "probable" CAA, and the antiplatelet treatment was discontinued.

At the age of 52, the patient came to our attention for diagnostic assessment of early-onset CAA. Amyloid-PET with flutemetamol was consistent with extensive amyloid deposition in the bilateral fronto-parieto-temporo-occipital regions. Genetic screening for *APP*, *PSEN1*, *PSEN2*, and *TTR* was negative; the *APOE* genotype was ε2/3. Lumbar puncture revealed reduced Aβ-42 (199, normal value >640 pg/mL), with normal TAU (196 pg/mL, normal value <450 pg/mL) and p-TAU (30.5, normal value <61 pg/mL). Neuropsychological testing showed mild deficits in memory and reasoning, with lexical difficulties (Mini-Mental State Examination corrected score: 26.9/30).

Two months later, the patient returned with recurrent episodes of paresthesias affecting the left face and arm. Neurologic examination was unremarkable. Brain MRI revealed a right parietal inflammatory lesion involving both subcortical white matter and cortex, with leptomeningeal enhancement; the SWI sequence showed multiple CMBs in both hemispheres and cSS in bilateral frontal and parietal lobes (Figure 5C). The findings were consistent with "probable" CAA-ri. The patient was started on corticosteroid therapy with oral prednisone 1 mg/kg/d for 2 weeks, progressively tapered and discontinued after 2 months.

During corticosteroid treatment, the patient reported remission of the transient neurologic episodes. A follow-up brain MRI assessed 2 months later confirmed the regression of the right parietal inflammatory lesion, without significant variations in the hemorrhagic load on the SWI sequence (Figure 5D). At the last follow-up 1 year later, the patient remained asymptomatic with a normal neurologic examination.

Case 6

In the mid-1980s, at the age of 24, this man sustained a severe concussive traumatic brain injury in a road accident, reporting a large bifrontal intraparenchymal hematoma and a severe cognitive impairment with frontal syndrome. Two months later, he underwent neurosurgery for the reconstruction of the facial massif and orbital floor. It is uncertain from the available clinical documentation whether any human-derived material was used.

At the age of 63, the patient was admitted to another hospital for an acute confusional state. Head CT scan showed a large right temporoparietal ICH and sequelae of previous bifrontal encephalomalacia (Figure 6A). Angio-CT scan was negative, and no brain MRI was performed at that time.

Four months later, the patient presented to our center for focal motor seizures, with tonic-clonic movements of the left limbs and contralateral head turning. On admission, neurologic examination revealed left hemiparesis with fluctuations of consciousness. Head CT scan was negative for acute lesions; EEG showed right temporal focal *status epilepticus* (eFigure 3A); lumbar puncture results were normal, including virologic investigations. The patient was treated with IV infusion of diazepam 10 mg, followed by levetiracetam 1,500 mg, valproate 1,500 mg, and lacosamide 400 mg. Despite treatment, seizures and right temporal lateralized periodic discharges (LPDs) persisted on EEG (eFigure 3B). He was then treated with phenytoin 1,500 mg, resulting in seizure control and marked reduction of epileptiform activity (eFigure 3C).

Brain MRI showed diffuse white matter vascular damage (Fazekas score 3), along with bilateral, asymmetric temporo-occipital hyperintense lesions, more pronounced in the right hemisphere (FLAIR sequence, Figure 6B), and bihemispheric CMBs and cSS (SWI sequence, Figure 6C). Overall, the clinical and instrumental findings were consistent with "probable" CAA-ri.

The patient was treated with IV methylprednisolone 1 gr/daily for 5 days, followed by oral prednisone 1 mg/kg/daily for 1 month, reporting a rapid and significant clinical and instrumental improvement. In particular, consciousness normalized and EEG showed progressive resolution of LPDs (eFigure 3D). A follow-up brain MRI 2 weeks after immunosuppressive therapy revealed partial regression of inflammatory lesions (FLAIR sequence, Figure 6D).

Given the suspicion of iCAA, further diagnostic investigations were performed. CSF analysis showed reduced Aβ-42 (120 pg/mL), increased TAU (889 pg/mL), and normal p-TAU (49.2 pg/mL). Genetic screening for *APP*, *PSEN1*, and *PSEN2* was negative; the *APOE* genotype was ε3/3.

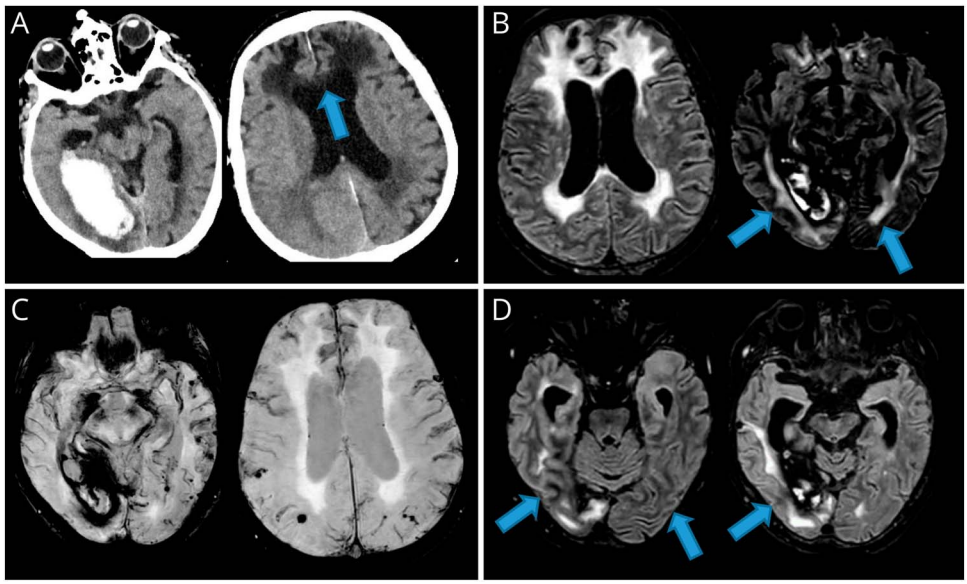
At the last follow-up, the patient exhibited a normal level of consciousness, frontal lobe syndrome, and mild left-sided hemisyndrome.

Discussion

In this work, we report a case series of patients with iCAA who developed clinical and radiologic features of CAA-ri. Our data highlight some peculiar characteristics of the recently reported iatrogenic form of the disease. In particular, some of the patients described here responded only partially to steroids, and in one case, we observed an inflammatory relapse shortly after the discontinuation of immunosuppressive treatment.

Moreover, while most cases presented typical clinical and instrumental characteristics of CAA-ri according to diagnostic criteria,[24] others showed less evident radiologic features, such as sulcal hyperintensity, recently emerged as a possible presentation of the disease.[25] Considering the poor prognosis of the patients described here, with 3 of 6 dying after the onset of CAA-ri, it is fundamental to carefully evaluate these radiologic aspects. This applies even to cases with only modest clinical

Figure 6 Neuroradiologic Features of Case 6



Head CT scan assessed at age 63 showing a large right temporoparietal ICH and sequelae of previous bifrontal encephalomalacia (A). Brain MRI revealing a diffuse vascular damage of the white matter (Fazekas score 3) and bilateral temporo-occipital hyperintense lesions (FLAIR sequence, B), along with bihemispheric CMBs and cSS (SWI sequence, C). Follow-up brain MRI 2 weeks after immunosuppressive therapy reporting partial regression of inflammatory lesions (FLAIR sequence, D). Arrows indicate the main radiologic characteristics. CMBs = cerebral microbleeds; cSS = cortical superficial siderosis; FLAIR = fluid-attenuated inversion recovery; ICH = intracerebral hemorrhage; SWI = susceptibility-weighted imaging.

symptoms,[26] which may be indicative of an early inflammatory process.

In this study, we observed a prolonged latency between the neurosurgical intervention (presumably involving exposure to Aβ) and the onset of CAA-ri. This finding is consistent with previous case series of iCAA diagnosed several years after neurosurgical procedures.[5-8,27]

The evidence that CAA may have an iatrogenic cause has only recently emerged and is likely still under-recognized in clinical practice.[5,7,8,28,29] The main difficulty in identifying iCAA cases lies in the clinical and radiologic features, which mostly overlap with those of sCAA. Although the earlier onset of symptoms could suggest a diagnosis of iCAA, as reported herein, patients can also have a later onset. It is reasonable to assume that the timing of neurologic symptom onset depends on the age at which patient underwent neurosurgery.

The pathogenic mechanisms underlying brain inflammation in patients with iCAA remain poorly understood. Early exposure to exogenous Aβ may promote premature vascular Aβ deposition and trigger perivascular neuroinflammation. This process involves reactive astrocytes and activated microglia, leading to impaired Aβ clearance and contributing to iCAA-related inflammatory manifestations.[30]

A recent multicenter international study described some peculiar neuroradiologic aspects of iCAA,[23] including deep CMBs, a high rate of the inflammatory component, and ICHs, with the distribution of hemorrhagic markers often ipsilateral to the presumed site of Aβ transmission.[31] In that cohort, neuroimaging signs of inflammation were identified in 27.4% of patients,[23] whereas in the present study only 15.8% of patients with iCAA developed CAA-ri. This discrepancy may be partly attributable to the different number of patients included in the 2 studies, but also to the diverse criteria of recruitment. While the former study evaluated the radiologic signs of brain inflammation, our work focused on the clinical and instrumental characteristics of CAA-ri.

The first patient with iCAA who developed CAA-ri was recently reported.[21] Notably, this case shares several features with those described in the present case series. In particular, the onset of inflammatory symptoms was characterized by focal epilepsy that was difficult to control with ASMs, rapidly progressing to *status epilepticus*. Moreover, CSF analysis revealed decreased Aβ levels with elevated total TAU and p-TAU, consistent with active neurodegeneration within the context of AD pathology. Clinical improvement was only partial after a prolonged course of corticosteroid therapy, and the patient experienced progression of both vascular burden and clinical deterioration, despite follow-up MRI showing a reduction in the inflammatory component.

In our case series, the available diagnostic findings allowed us to classify 3 cases as "possible" iCAA. In particular, cases I and II showed a rapid clinical deterioration leading to death, and it was not possible to perform the necessary investigations to further support the diagnostic hypothesis of iCAA. Notably, case 4 was observed before the publication of the Queen Square criteria.[8] For this reason, the anamnestic information regarding previous neurosurgical intervention was not adequately evaluated, and the patient did not undergo further diagnostic investigations to verify Aβ accumulation in the CNS or to rule out a genetic nature of the disease. Conversely,

more in-depth investigations allowed us to define the remaining 3 cases as "probable" iCAA. For these cases, we identified reduced CSF Aβ levels, and in 2 patients, we confirmed the absence of a genetic cause of the disease.

Our observations also confirm that both symptomatic seizures and epilepsy represent a common clinical manifestation of CAA. In particular, 4 patients experienced epileptic seizures during the acute phase of CAA-ri, and another patient had focal seizures as the main manifestation of iCAA. This is consistent with recent evidence showing that CAA is frequently associated with epilepsy,[32] particularly in the context of CAA-ri.[33]

This study has some limitations. First, we identified a small number of patients. However, these conditions are extremely rare. To increase the sample size, the study included centers with extensive experience in CAA. This could also represent a potential limitation of the study. Because the institutions participating in this research are referral centers for the diagnosis and treatment of CAA, it is possible to hypothesize a selection bias toward the most severe cases.

Second, owing to a retrospective collection of cases from different institutions, patients were characterized and treated using nonstandardized methods and protocols.

Third, none of the cases reported here had a histologic confirmation of the disease. Furthermore, the diagnosis of iCAA was based on proposed diagnostic criteria not yet validated. Moreover, owing to limitations in the available clinical documentation, for both cases IV and VI, we were unable to retrieve information regarding the possible use of human-derived material during the neurosurgical procedures. However, based on the nature of the surgeries, it is plausible that such material was used.

Fourth, in the differential diagnosis of cases I and VI, we considered that brain hyperintense lesions involving areas of the right hemisphere could be at least partly secondary to the undergoing focal *status epilepticus*.[34] However, the presence of several elements suggestive of CAA, as brain hemorrhagic lesions, along with the clinical-instrumental response to steroid treatment, made the diagnosis of CAA-ri more likely.

This study further expands our knowledge of CAA, confirming that it is not a single disease but can have different modalities of presentation.[35]

The association of iCAA with CAA-ri confirms the aggressive nature of the iatrogenic variant of the disease. Accordingly, iCAA should be promptly recognized by clinicians, and patients should undergo close clinical and radiologic follow-up. In these patients, the detection of brain inflammation may allow for rapid initiation of immunosuppressive treatment, even if it remains to be established whether this approach results in significant clinical benefit.

In this case series, the development of CAA-ri in patients with an iatrogenic cause of the disease was associated with a rapid and severe clinical course, often resulting in a short-term fatal outcome. Contrary to what has been reported for sCAA,[15,36] CAA-ri in patients with iCAA seems to respond only partially to steroid treatment.

The role of neuroinflammation in CAA remains poorly understood.[37] However, it is conceivable that in iCAA, the presence of exogenous Aβ may act as a trigger for the activation of inflammatory pathways, ultimately leading to the development of CAA-ri. Future studies will be necessary to clarify these aspects, which will also be useful for better understanding of the pathogenesis of iCAA and for providing specific monitoring and therapeutic strategies for these patients.

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Author Contributions

B. Storti: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. G. Negro: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. G. Orsani: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. P.T. Damavandi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Donelli: major role in the acquisition of data. E. Cavarsaschi: major role in the acquisition of data. E. Conti: Major role in the acquisition of data. G. Sala: major role in the acquisition of data. C.P. Zoia: major role in the acquisition of data. C. Ferrarese: drafting/revision of the manuscript for content, including medical writing for content. M. Stanziano: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. I. Canavero: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Bersano: drafting/revision of the manuscript for content, including medical writing for content. J.C. DiFrancesco: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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