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Multiple Intracerebral Hemorrhages in an Old Patient with Rheumatoid Arthritis

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A 78-year-old Caucasian man was admitted in the Department of Neurology for visual disturbances, started two days before. The next day the patient experienced headache, fever and gait disturbances. He had hypertension, diabetes mellitus, an ischemic stroke 13 years ago, longstanding seronegative rheumatoid arthritis (17 years), polynodular goiter, right ischio-pubian fracture and right femoral vein thrombosis a year ago due to a car accident, since he is treated with oral anticoagulants associated to antiaggregant, hypotensors, statin and oral antidiabetics. The neurologic examination had evidenced nuchal rigidity, left homonymous hemianopsia, left central facial palsy, ataxia of the inferior limbs with wide-based gait, achilean reflexes abolished bilaterally, bilaterally abolished plantar reflexes, ideomotor apraxia, dysarthria, hypoprosexia, and preserved consciousness patient. A non-contrast cerebral CT scan had shown right temporal and parieto-occipital intraparenchymatous hemorrhages, a right frontal sequelar lesion, multiple old lacunar infarcts, cortical atrophy. Laboratory findings included an inflammatory syndrome, absence of rheumatoid arthritis positive serology, normal coagulogram, an elevated proteinuria. The cerebral IRM performed on the seventh day of hospitalisation was suggestive for subacute right parietal hemorrhage, old cerebral infarction in the right anterior cerebral artery area, old lacunar infarcts and cerebral atrophy. The anticoagulant and antiaggregant treatment was stopped after a generalized tonic-clonic seizure occurred. Antiedematous, hypotensor, anticonvulsivant, beta-blocker, and symptomatic treatment was started, while the antidiabetic treatment was continued. All symptoms remitted. Arguments for amyloid angiopathy in our patient are previous non-cardioembolic ischemic stroke and a chronic inflammatory disease-rheumatoid arthritis in his personal medical history.

Key words: Multiple simultaneous intracerebral hemorrhages, rheumatoid arthritis, amyloidosis.

INTRODUCTION

Multiple simultaneous intracerebral hemorrhages are a rare type of stroke. Primary multiple simultaneous intracerebral hemorrhages are defined as two discrete primary intracerebral hemorrhages occurring simultaneously or within 24 h since the first identified intracerebral hemorrhage [1].

Ten to twenty percent of all strokes are spontaneous intracerebral haemorrhages [2, 3].

The incidence of multiple simultaneous intracerebral haemorrhages is up to 5.6% of all spontaneous intracerebral hemorrhages. Multiple simultaneous intracerebral haemorrhages occur more commonly in a second form [1], and primary multiple simultaneous intracerebral haemorrhages have a much lower incidence varying from 0.75 to 3.0% of all cases of spontaneous intracerebral hemorrhage [1, 4]. As for the possible mechanism behind the development of simultaneous/multiple hypertensive hemorrhages, some authors suggested that the bleeding might have occurred simultaneously in different regions of the brain, or that the initial bleeding was followed after a short time by a secondary one at another site due to high intracranial pressure and circulatory disturbance [4, 5].

The overall outcome and prognosis are also poorer than with primary solitary intracerebral haemorrhages.

Intracerebral hemorrhage is an important clinical condition leading to severe disability and a high mortality rate. In case of survival, patients have higher favourable outcome.

CASE REPORT

A 78-year old Caucasian man was admitted in the Department of Neurology for visual disturbances, started two days before. He had not visited a doctor. The next day he experienced headache, fever and afterwards gait disturbances with staging movements and wide-based gait.

We have noticed in his medical history hypertension, diabetes mellitus, an ischemic stroke

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13 years ago, longstanding seronegative rheumatoid arthritis (17 years), polynodular goiter, right ischiopubian fracture and right femoral vein thrombosis a year ago due to a car accident, he received treatment with oral anticoagulants associated to the previous treatment with antiaggregant, hypotensors, statin and oral antidiabetics.

He was no smoker and he consumed alcohol only occasioanally.

The patient presented at the Emergency Department of the Bucharest University Emergency Hospital. His blood pressure was 165/95 mm Hg.

The neurologic examination had emphasized nuchal rigidity, left homonymous hemianopsia, left central facial palsy, right facial constitutional asymmetry mimicking peripheral facial palsy, no motor deficit, ataxia of the inferior limbs with wide-based gait, achilean reflexes abolished bilaterally, no flexion of plantar reflexes bilaterally, ideomotor apraxia, dysarthria, hypoprosexia, preserved consciousness, and he was self-and temporo-spatially oriented.

A non-contrast cerebral CT scan was performed. It had shown right temporal and parieto-occipital intraparenchymatous haemorrhages, a right frontal sequelar lesion, multiple old lacunar infarcts, cortical atrophy (Figure 1). He was referred to our Department of Neurology.

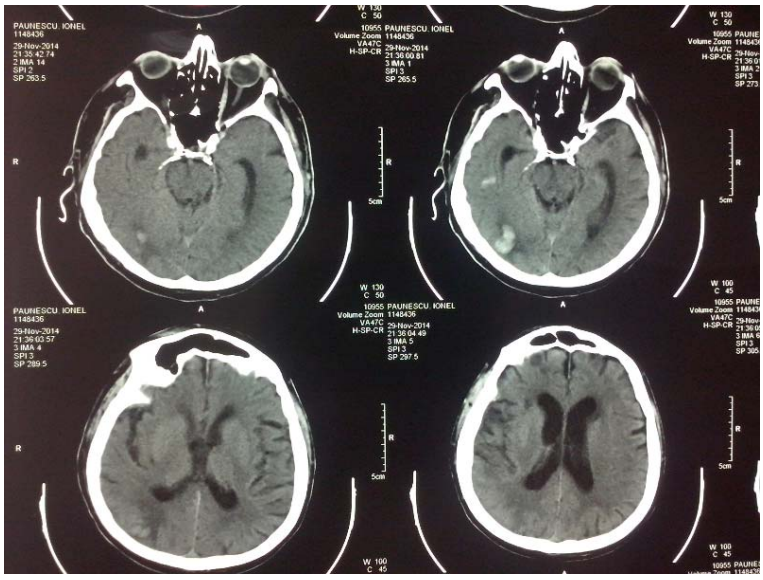

Figure 1. Cerebral CT scan-Right temporal and parieto-occipital intraparenchymatous hemorrhages, a right frontal sequelar lesion, multiple old lacunar infarcts, cortical atrophy.

At the admittance, clinical examination revealed a body temperature of 37^{8} degrees Celsius, venous ectasias of the inferior limbs, facial telangiectasias, bilateral conjunctival hyperemia, bilateral carotid bruit, the BP was 165/95 mm Hg.

The neurologic examination was the same as the previous one.

The blood tests have shown an inflammatory syndrome, absence of rheumatoid arthritis positive serology, normal coagulogram with an INR of 1.34. The urine examination was normal, excepting a proteinuria of 1200 mg/24 h.

The ECG had evidenced synusal rhythmus, QRS axis at 0 degrees, non-specific signs of repolarisation in inferior derivations, left atrial loading.

The EEG did not reveal abnormalities.

The ultrasound examination of cervico-cerebral arteries had shown bilateral carotid atheromathosis.

The cardiac ultrasound examination was normal.

The cerebral IRM performed on the seventh hospital day was suggestive for subacute right parietal hemorrhage, old cerebral infarction in the right anterior cerebral artery area, old lacunar infarcts and cerebral atrophy (Figure 2).

The cardio-pulmonary X-ray examination had shown bilateral diffuse interstitial abnormalities and enlarged vascular hills.

During the clinical course, the patient presented a generalized tonic-clonic seizure.

The anticoagulant and antiaggregant treatment was stopped. An antiedematous, hypotensor, anticonvulsivant, beta-blocker, and symptomatic treatment was commenced, while the antidiabetic treatment was continued.

Repeated cerebral CT scan after 14 days from the onset had shown the remission of right hemispheric cerebral hemorrhages (Figure 3).

The patient gradually improved, with remission of the initial symptoms, of seizures and of fever.

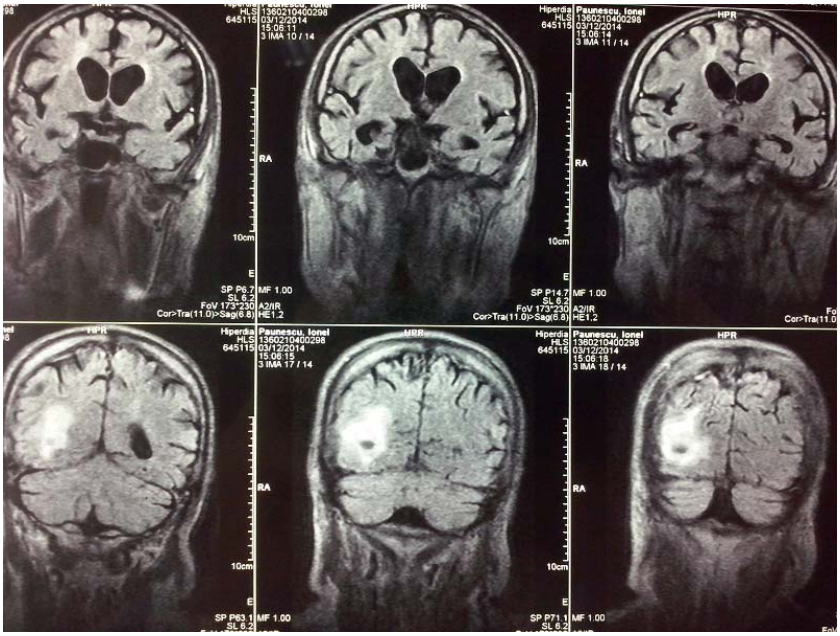

Figure 2. Cerebral IRM (FLAIR)-Subacute right parietal hemorrhage, old cerebral infarction in the right anterior cerebral artery area, old lacunar infarcts and cerebral atrophy.

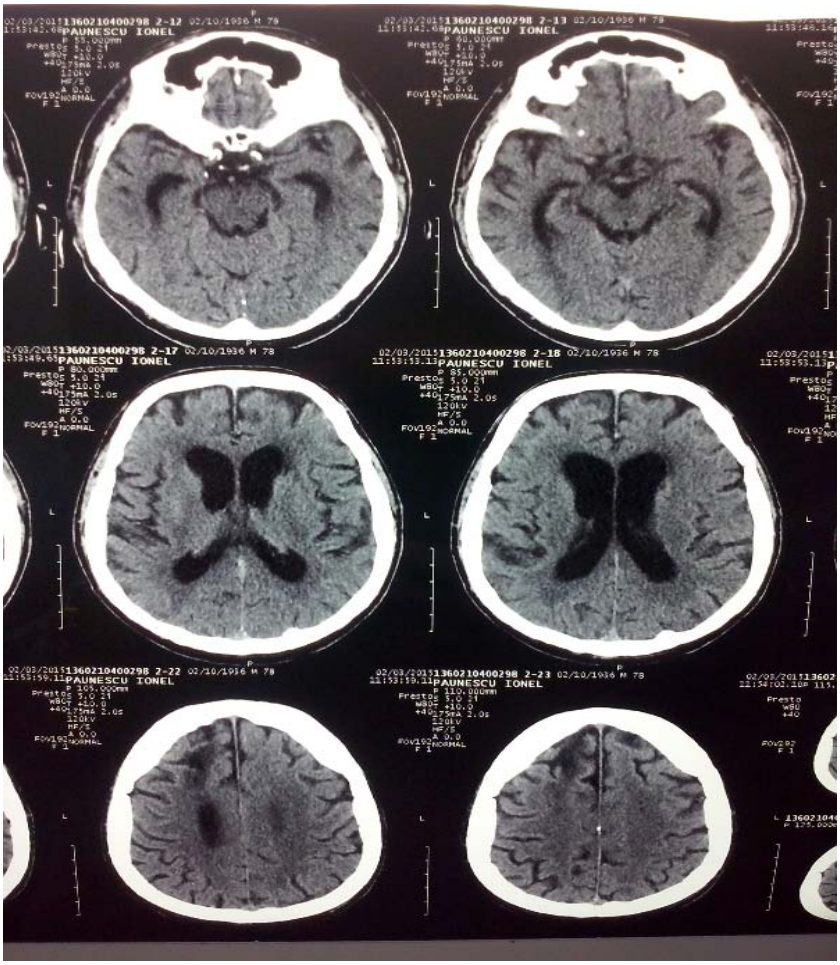

Figure 3. Cerebral CT scan after 14 days-Remission of right hemispheric cerebral hemorrhages.

DISCUSSION

The question raised in this case is what was causing the hemorrhages?

We have ruled out a coagulopathy (spontaneous or induced by anticoagulant therapy) while APTT, INR and platelet count were all normal.

The two main causes of primary intracerebral hemorrhage are hypertensive vasculopathy and cerebral amyloid angiopathy (CAA) [3, 6].

Hypertension and CAA have widespread effects on the cerebral vasculature and autoregulation mechanism.

Chronic and long-standing hypertension causes hyperplastic arteriosclerosis, leading to fragile vessels [7].

There are few hypotheses regarding possible mechanisms in the context of a widespread fragile cerebral vasculature and impaired autoregulation mechanism. A first mechanism was proposed in 1995 [4, 7], the second one in 2005, suggesting that the initial hemorrhage causes a reflex increase in blood pressure and intracranial pressure, resulting in bleeding in other brain areas [7].

A third possible mechanism was proposed in 2011 and it was similar to the second mechanism. With the hemorrhage-induced pain and coinciding release of catecholamines, hypertension worsens, thereby causing additional hemorrhage in diseased vessels [8].

Hypertension is still the most important etiological factor for simultaneous multiple intracerebral haemorrhages. The widespread and prolonged degeneration of intracerebral areterioles predisposes patients to the development of multiple intracerebral haemorrhages. In a study regarding this subject, only hypercholesterolemia was identified to be significantly associated with this unusual brain event [9].

The location of the intracerebral hemorrhages of our patient was not the right one for a hypertensive bleed (putamen, thalamus, pons) [9-11].

In the metaanalysis of primary multiple simultaneous intracerebral haemorrhages the authors have observed that the hematomas were most commonly located in the basal ganglia (45.83%), followed by the thalamus (30.56%), cerebellum (10.19%), lobar region (7.41%) and brain stem (6.21%), including the midbrain and the pons. Bilateral primary multiple simultaneous intracerebral haemorrhages were also commonly found (18.1%), while bilateral lobar and cerebellar hemorrhage were least commonly encountered and have been identified in only 1 case each (0.95%). Unilateral primary multiple simultaneous intracerebral haemorrhages were encountred in 46.67% of cases [12, 13].

The finding of symmetric simultaneous hypertensive putaminal or thalamic haemorrhages suggests that patients may have symmetrically vulnerable vessels [14].

If an intracerebral hemorrhage occurs, acute cerebrovascular changes are subsequently produced. It could mean that hemodynamic change of the parent vessel can have a simultaneous effect on its perforators. Or, it is possible to assume that one area of bleeding and probable surge of regional pressure induce secondary bleeding in adjacent areas within a short period [15].

Vessel irregularities, such as strengthened jet flow, can occur in vulnerable penetrating arteries and could cause a subsequent intracerebral hemorrhage [16].

Cerebral amyloid angiopathy (CAA) is defined by the accumulation of amyloid in the walls of small-and medium-sized cerebral arteries.

One of the most frequent complications of CAA is spontaneous, often recurrent intracerebral hemorrhage. Amyloid deposition in cerebral blood vessel can weaken the vessel wall, causing rupture and intracerebral hemorrhage. CAA-related hemorrhage accounts for 5-20% of all spontaneous cerebral haemorrhages in elderly subjects, though intracerebral hemorrhage was found only in 5.4% of autopsy-confirmed CAA [17].

In the case of amyloidosis associated with chronic inflammatory disease (AA amyloidosis), AA amyloid fibrils are derived from cleavage fragments of the circulating acute-phase reactant SAA protein. SAA is an apolipoprotein of high-density lipoprotein which, like C-reactive protein, is synthesized by hepatocytes under the transcriptional regulation of cytokines including interleukin (IL-1, IL-6) and tumor necrosis factor (TNF) [18].

Rheumatic diseases, such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and juvenile idiopathic arthritis are the most frequent causes (70%) of AA amyloidosis.

The prevalence of the asymptomatic phase of AA in amyloidosis in rheumatoid arthritis can range between 0.5-14% [19].

The predominant feature at diagnosis of AA amyloidosis is renal dysfunction, manifest as proteinuria, or renal failure. The development of proteinuria in a patient with rheumatoid arthritis should always raise the suspicion of AA amyloidosis. Goiter can be a sign of AA amyloidosis [20].

Noninvasive diagnostic criteria have been developed to reliably diagnose CAA during life [21].

The diagnosis of amyloidosis requires the histological demonstration of amyloid deposits. The abdominal fat pad is the safest and most common biopsy site, while rectal mucosa and labial salivary glands are seldom the target of biopsy. Abdominal subcutaneous fat aspiration (ASFA) detects amyloid deposits in patients with all types of amyloidosis with a sensitivity ranging from 57% to 88% and a specificity of 100% [22].

CAA is considered "probable with supporting pathology" when, in combination with appropriate clinical data, pathologic tissue from a biopsy performed at the time of hematoma evacuation reveals amyloid angiopathy, CAA is considered "probable" if there is an appropriate clinical history as well as imaging findings of multiple cortical-subcortical hematomas in a patient 55 years old or older, with no other clinical or radiologic cause of hemorrhage. Clinical data suggesting CAA and the imaging finding of a single cortical-subcortical hematoma in a patient older than 55 years, without other causes of hemorrhage, leads to a diagnosis of "possible" CAA.

The hallmark of CAA hemorrhage is lobar, cortical, or cortical-subcortical cerebral haemorrhages, affecting normotensive individuals, over age 55, frequently multiple, recurrent, which can extend from the cortex to the subarachnoid space or, less commonly, to the ventricle. The localization of CAA hemorrhage follows the localization of CAA in the cerebral cortex and cortico-subcortical or lobar regions.

Prior microhemorrhage burden, perhaps due to severity of hypertension or cerebral amyloid angiopathy, may mark patients at risk for primary multiple spontaneous intracerebral hemorrhages occurrence [23].

The diagnosis of CAA should be considered when patients present with reversible white matter lesions and multiple cerebral microbleeds simultaneously [24].

The CAA is the most common cause of lobar parenchymal hemorrhage in the elderly. It should be considered in normotensive patients with multiple or superficial intracerebral hemorrhage, particularly when the patient is demented with a history of hemorrhagic stroke [25-28].

Most of these haemorrhages are petechial hemorrhages (microhemorrhages). CT and conventional or fast spin-echo T1-and T2*-weighted MR imaging sequences are relatively insensitive for each small haemorrhage. Local magnetic field inhomogeneity related to the presence of hemosiderin in foci of microhemorrhages causes a marked loss of signal a T2*-weighted gradient echo (GRE) imaging, which is currently the most sensitive sequence for detection of the cortical-subcortical microhemorrhages associated with CAA. More recently, positron emission tomographic imaging with the β-amyloid-binding compound Pittsburgh Compound B (PiB) has been reported as a reliable technique to detect cerebrovascular β-amyloid and a method for identifying the extent of CAA in living subjects [29].

Arguments for amyloid angiopathy in our patient are previous non-cardioembolic ischemic stroke, a chronic inflammatory disease-rheumatoid arthritis in his personal medical history and the presence of goiter.

Additional imaging is necessary to evaluate ischemic stroke *vs* hemorrhagic conversion, arteriovenous malformations or ruptured aneurysms, bleeding tumor and previous bleeds.

Head and neck MRI/MRA provide information on each of these possibilities. High signal on DWI in the lesional surrounding area (reduced diffusion) seems consistent with ischemic stroke, but hemorrhage interferes with DWI signal.

If MRA did not show any vascular malformation, performing a cerebral angiography must be done, it is the gold standard.

Cerebral venous thrombosis usually causes hemorrhagic infarction and discrete haemorrhages are not uncommon [30].

We excluded the diagnosis of cerebral venous thrombosis indirectly, because the renal function did not permit contrast administration, and because the patient did not worsen when the anticoagulant and antiaggregant treatments were stopped.

Bleeding tumors (<20% primary brain tumors, >80% metastatic) is another possible differential diagnosis [31].

Frequent episodes of bleeding from malignant tumors rarely occur in different intracranial regions in the subacute period [32-34].

Characteristic CT scan findings included: a neoplastic core (high or low density), small, multifocal, clots usually at the margin of the tumor; and surrounding, often extensive, edema. Enhancement of the tumor tissue with contrast medium is observed in most cases, the regions which are enhanced have a peripheral distribution corresponding to the site of hemorrhage [35].

For any suspected brain tumor, the imaging modality of choice is MRI with gadolinium enhancement. It is necessary to look for enhancement on T1.

For solitary brain lesions, in order to rule out metastasis, a screening for the primary may be done: chest X-ray (lung is primary in approx. 50%), mammogram (breast is primary in 15-20%), abdominal CT (renal and colon approx. 5-10% each), skin examination (melanoma approx. 5-10%), 10% primary never found [36].

Trauma is another cause of multiple intracerebral hemorrhages, but our patient did not present such events. Traumatic intracerebral hemtomas are most common in the frontal and temporal lobes, often associated with cortical contusions and lacerations, or situated beneath skull fractures, they tend to be irregular in contour, poorly demarcated, and non-uniform in density.

Cerebral vasculitis in rheumatoid arthritis is a rare entity. It is similar to that of other collagen diseases but acute fibrinoid necrosis has been encountered less commonly [37].

Intracerebral hemorrhage is a known complication of cerebral vasculitis, although its incidence is low. Usually the course is fatal, in some cases the clinical recovery is total [38].

Some drugs as cocaine abuse are involved in the pathogenesis of multiple intracerebral haemorrhages, but our patient was not a drug consumer [39].

After smoking "crack" cocaine, multiple intracerebral hemorrhages may occur. Cocaine presumably induces an acute rise in blood pressure or vasoconstriction, hemorrhage might then result from an acute increase in blood flow once the vasospasm subsides, rupturing vessel walls that were subjected to ischemic damage [40].

A new drug-recombinant human activated protein C (DAA) (Dotrecogin Alpha) has been recently reported to reduce mortality in severe sepsis [41]. The most important causes of mortality in sepsis are diffuse endovascular damage, coagulopathy, and multiple organ failure [42, 43]. Dotrecogin Alpha (activated) could cause serious bleeding due to its anticoagulants and profibrinolytic effects [44]. Intracranial bleeding could occur in patients under DAA treatment, even though platelet number and bleeding test findings are normal.

Administration of intravenous tissue plasminogen activator could be a causative bleeding factor. Hemorrhagic transformation on CT (mean 24 hours after onset) was seen in 27% subjects [45].

The volume of ischemic tissue estimated in terms of ASPECTS-DWI score appears to be a useful marker for predicting hemorrhagic transformation [46, 47].

Herpes virus encephalitis or vasculopathy is a rare cause of multiple intracerebral hemorrhages and must be considered in the differential diagnosis of patients presenting with an acute history of fever, altered consciousness, and focal neurologic deficits with history of a typical herpetic rash [48].

The exact pathophysiology of primary multiple simultaneous intracerebral hemorrhages remains unclear.

Poorer outcome in patients with multiple simultaneous intracerebral haemorrhages can be explained by the concomitant destruction of crossing and non-crossing fiber tracts and bilateral diaschisis phenomenon.

In general, the prognosis is poor both on short-term and long-term. If the neurological grading is 1-3 at the time of presentation, the outlook is usually good whether conservative or surgical treatments were used; if this grading is 4-5, the prognosis becomes poor no matter which treatment modality is used [49].

CONCLUSIONS

1. Arguments for amyloid angiopathy in our patient are previous non cardioembolic ischemic stroke and a chronic inflammatory disease-rheumatoid arthritis in his personal medical history.

2. Previous bleeds are an argument in favour of amyloid angiopathy

3. In most cases, the exact pathophysiology of primary multiple simultaneous intracerebral haemorrhages remains unclear.

Un pacient de 78 de ani a fost internat în Clinica de Neurologie pentru tulburări de vedere care au început cu două zile în urmă. Ziua următoare pacientul a prezentat cefalee, febră şi tulburări de mers. Ca antecedente personale patologice prezenta HTA, diabet zaharat, un stroke ischemic în urmă cu 13 ani, poliartrită reumatoidă seronegativă cu evoluție îndelungată (17 ani), guşe

polinodulară, fractură ischiopubiană dreaptă şi tromboză a venei femurale drepte în urmă cu un an post accident de maşină, de când urmează tratament cu anticoagulante orale asociate cu antiagregante, hipotensoare, statină şi anti-diabetice orale. Examenul neurologic a evidenţiat redoarea cefei, hemianopsie laterală homonimă stângă, paralizie facială stângă de tip central, ataxia membrelor inferioare cu mers cu bază de susţinere lărgită, reflexul achilian abolit bilateral, indiferenţă plantară bilaterală, apraxie ideomotorie, dizartrie, hipoprosexie şi stare de conştienţă păstrată. Examenul CT cerebral nativ a evidenţiat hemoragii intraparenchimatoase temporale şi parieto-occipitale drepte, o leziune frontală dreaptă sechelară, multiple infarcte lacunare vechi, atrofie corticală. Datele de laborator au relevat sindrom inflamator, absenţa serologiei pozitive pentru poliartrită reumatoidă, coagulograma normală, proteinurie crescută. IRM cerebral efectuat în a şaptea zi de spitalizare a fost sugestiv pentru hemoragie parietală dreaptă subacută. Tratamentul anticoagulant şi antiagregant a fost oprit după survenirea unei crize convulsive tonico-clonice generalizate. S-a iniţiat tratament antiedematos cerebral, hipotensor, anticonvulsivant, betablocant şi simptomatic şi a fost continuat tratamentul antidiabetic. Toate simptomele s-au remis. Argumentele pentru angiopatie amiloidă la pacientul nostru sunt stroke-ul ischemic necardioembolic în antecedente şi o afecţiune inflamatorie cronică-poliartrita reumatoidă în antecedentele personale patologice.

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