Massive cortico-subcortical ischemic stroke with a consecutive hemorrhagic event: a case report

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Abstract
Background: We report a case of a 78-year-old woman with a large cerebral infarction probably due to athermanous embolism following atrial fibrillation. Case description: The patient, known with atrial fibrillation, high blood pressure and heart failure, complained of headache and motor impairment on the left side of the body. CT imaging revealed a subacute ischemic lesion in the right fronto-occipital lobes, and an old ischemic lesion in the right fronto-parietal lobes. Anticoagulant treatment was conducted with careful monitoring of the coagulability status. After almost three weeks, suddenly the patient became comatose and died shortly after. Macroscopic and microscopic examination confirmed the cortico-subcortical ischemic lesions, but also identified a fresh hemorrhagic site in pons, distant from the initial lesion sites. An immunohistochemical study identified blood vessels in the ischemic sites completely isolated from any glial support.

Conclusions: This is a rare case of a large cerebral infarction with a pontine hemorrhagic event.

Keywords: ischemic stroke, hemorrhage, distant hemorrhagic event, necrosis-resistant endothelial cells.

Introduction
Stroke is the second leading cause of mortality worldwide, and the first cause of invalidity among the surviving patients [1]. Large hemispheric ischemic strokes represent around 5% of all ischemic strokes, and the main cause of death is massive edema developed after such an episode, especially if this was the result of a medial cerebral artery occlusion [2].

Although edema is the most fearful complication of a stroke, hemorrhagic transformation do occur but usually are not considered to worsen the outcome of the disease unless they occur in a vital center [3]. Actually, it is not known what percent of the hemorrhages appear in fact from a hemorrhagic transformation in an existing ischemic area [1]. Anticoagulant therapy is currently a most profitable option for patients with acute ischemic stroke, but this treatment also carries an important risk of secondary hemorrhage, especially on a background of hypertension, coagulability deficiencies and a plethora of familial inherited diseases. However, hemorrhagic events distant from the ischemic sites are known to occur, but not much data is known to explain their apparition [4].

At the tissue level, it is well known that neurons are more sensitive to hypoxia compared to glial cells, and to vascular endothelial cells, but to what extent this phenomenon is implicated in stroke pathophysiology is not known [5–7]. Astrocytes have been known to protect against opening the blood brain barer in hypoxic conditions [8], and would be thought to occur wherever impaired vessels are. However, apparent intact vessels in the infarct core, completely missing any glia limitans have not been reported in the literature to our knowledge yet.

In this report, we present the case of a patient surviving after two large cortico-subcortical ischemic strokes, but dying immediately after a pontine hemorrhagic lesion; and we discuss the finding of glial void vessels still present in the lesion core.

Materials, Methods and Results
Clinical and imaging data
Patient M.D., female, aged 78 years, known with cardiac pathology (atrial fibrillation, type III high blood pressure, dilatative cardiomyopathy, and NYHA class II heart failure), is presented in the Neurology Clinic,
University of Medicine and Pharmacy of Craiova, for headache and motor impairment on the left side of the body, both occurred suddenly during the same morning. A neurological examination at admission showed plegic motor deficit of the left side of the body, hypotony at the same level, left homonymous hemianopsia, and sensibility loss, the patient being confuse and sleepy. Before admission in the hospital, the patient followed a treatment with oral anticoagulants and tonocardiacs, coagulation times being normal during the hospitalization.

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Native brain CT scan performed at 24 hours from admission showed a hypodense area of appreciatively 62×30 mm on the right fronto-parieto-occipital lobes with an aspect of a subacute ischemic lesion; an old sequelar lesion of 36×20 mm in the right fronto-parietal lobes, paraventricular (Figure 1, A and B). There was also noted a cortical atrophy with internal hydrocephaly, while the ventricular system was not deviated from the midline.

During the hospitalization time, the treatment consisted of hyperosmolar solutions, anticoagulants and symptomatic treatment; under these circumstances, the clinical evolution was stationary for 18 days. In the 19th day, the symptomatology worsen very rapidly (entering a comatose state), and for that reason a CT scan was repeated – with no hemorrhage being observed (an acute ischemic lesion typically cannot be visualized before 72 hours from the onset with our CT setup). Shortly after, in the same day, the patient deceased.

**Morphopathology**

Upon brain prelevation, macroscopic observation identified relative retracted and atrophied gyri at the level of the right fronto-tempo-parietal region. A moderate softening was noted in the cortex of the right superior occipital lobe. The rest of the telencephalon and the hindbrain showed no obvious macroscopic changes. On coronal slices, the right hemisphere had an old scar at the level of the superior frontal lobe, atrophy and loss of the gray-white matter demarcation at the level of the insular lobe, parietal lobe, and recent lesions (as tissue softening) of the hippocampus (Figure 1, C and D) and superior occipital lobe (data not showed). Substantia nigra had a normal pigmentation. On sectioning the pons, multiple hemorrhagic lesions could be noted (data not showed).

**Figure 1** – (A) Horizontal CT scan showing a hypodense silhouette at the level of the temporo-parieto-occipital lobes; (B) A more cranial horizontal CT scan illustrating a marked atrophy at the level of the right insular lobe (older lesion); (C) A coronal section at the level of the internal capsule and the head of the caudate nucleus showing an old yellowish scar at the level of the right superior frontal lobe and the atrophy and loss of gray-white matter at the level of the right insula (arrow); (D) Another coronal section at the level of the ventral posterior lateral thalamic nucleus showing softening of the right hippocampus.

After macroscopic diagnosis, fragments from the patient’s brain were harvested and fixed in 10% neutral buffered formalin for 10 days. These included all major cortical and subcortical areas as well as any observed lesion together with a contra-lateral fragment. All the material is part of the brain bank currently under development because of the collaboration between the Departments of Histology, Pathology and Neurology, University of Medicine and Pharmacy of Craiova. After fixation, the tissue was routinely processed for paraffin inclusion, and serial 5 µm thick sections were cut on a rotary microtome and collected on poly-lysine coated slides. Sections were stained for Hematoxylin and Eosin or processed for immunohistochemistry.

**Figure 1** – (A) Horizontal CT scan showing a hypodense silhouette at the level of the temporo-parieto-occipital lobes; (B) A more cranial horizontal CT scan illustrating a marked atrophy at the level of the right insular lobe (older lesion); (C) A coronal section at the level of the internal capsule and the head of the caudate nucleus showing an old yellowish scar at the level of the right superior frontal lobe and the atrophy and loss of gray-white matter at the level of the right insula (arrow); (D) Another coronal section at the level of the ventral posterior lateral thalamic nucleus showing softening of the right hippocampus.

On Hematoxylin–Eosin slides, on the overall there was a moderate vacuolation of the superficial to middle cortical layers. The area identified on macroscopy as a yellowish old ischemic scar proved indeed under the microscope to be composed mostly of gemistocytic astrocytes, with ballooned eosinophilic bodies, eccentric nuclei and short, blunt extensions (Figure 2, A and B). This gliotic scar surrounded cavitations, and in some of them spumous macrophages could still be identified. In the superior right parietal and occipital lobes, more recent ischemic lesions could be identified as the tissue was completely replaced by liquefaction necrosis and there was no cavitation yet. Interestingly, this affected mostly the white matter, with a strong gliotic reaction at
the white-gray matter boundary (Figure 2C). Particular
to this area, all cortical layers were heavily vacuolated.
A cholesterol granuloma was identified in the parietal
lobe, comprising cholesterol clefts surrounded by
liquefied tissue, epithelioid cells, foamy macrophages
and mononuclear inflammatory cells (Figure 2D).

Figure 2 – (A) Cystic cavity formed after an old infarction; (B) Enlarged region from image (A) showing the
persistence of foamy macrophages in the cavity and the gemistocytic astrocytes limiting the cavity on the parenchymal
side; (C) Panoramic view of a gyrus from the parietal lobe where all the white matter has suffered a liquefactive
necrosis, also there is a strong gliotic response at the limit between white and gray matter; (D) A cholesterol
granulomatous reaction in the superior parietal gyrus; with foamy macrophages, epithelioid cells, mononuclear
inflammatory cells and liquefied tissue. Scale bars represent 50 µm.
Small newly formed vascular lumens were observed around the cholesterol clefts, and overall no remaining of the original vessel could be identified. Striatum showed a minor degree of vacuolation and a small old ischemic lesion (with foamy macrophages and cavitation) could be identified in the right ventral postero-lateral thalamic nucleus, just beneath the ependima. There was also a rarefaction of the hippocampal dentate gyrus granular cells, as well as of the pyramidal cells in the hippocampus proper (Figure 3A). A large number of corpora amylacea were observed in periventricular areas (and especially in thalamus and hippocampus), and around hyalinised blood vessels. Fresh petechial or larger hematic extravasations could be described at the level of pontine tegmentum, paralleling the macroscopic observations (Figure 3B). This did not involve the anterior pontine areas and neither extended to mesencephalon or medulla. At the level of medulla, the large motor neurons of the hypoglossal nucleus showed only a moderate chromatolysis (Figure 3C).

Figure 3 – (A) Panoramic view of the anterior hippocampus with dentate gyrus granular cell loss and white matter spongiosis, as well as the loss of pyramidal neurons in the CA4 region; (B) Hemorrhages and tissue vacuolation in the pontine periventricular wall; (C) Neuronal ballooning and chromatolysis in the motor neurons of the hypoglossal nucleus. Scale bars represent 50 µm.

**Tissue processing for immunohistochemistry**

Briefly, after antigen retrieval, sections were cooled to room temperature and incubated for 30 minutes in a 1% hydrogen peroxide solution. Sections were next washed in PBS, followed by a blocking step of 30 minutes in 1% skim milk. A panel of primary antibodies was selected in order to characterize vascular, macroglial and astroglial compartment, as well as neurodegeneration-specific targets (Table 1).
Table 1 – The antibodies used in this study

<table>
<thead>
<tr>
<th>Name</th>
<th>Clonality</th>
<th>Epitope</th>
<th>Dilution</th>
<th>Retrieval</th>
<th>Source</th>
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<tr>
<td>4G8</td>
<td>Mouse, IgG1</td>
<td>Amino acids 17–24 of Aβ</td>
<td>1:30 000</td>
<td>Formic acid</td>
<td>Chemicon, Medicalkit, Craiova</td>
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<tr>
<td>AT8</td>
<td>Mouse, IgG1</td>
<td>Tau protein phosphorilated at S202 / T205</td>
<td>1:1000</td>
<td>–</td>
<td>NanuTec, Medicalkit</td>
</tr>
<tr>
<td>CD31</td>
<td>Mouse, IgG1k</td>
<td>Vascular endothelium</td>
<td>1:100</td>
<td>0.1 M Citrate pH 6</td>
<td>Dako, Medicalkit</td>
</tr>
<tr>
<td>CD68</td>
<td>Mouse, IgG1k</td>
<td>Macrophages, monocytes</td>
<td>1:100</td>
<td>0.1 M Citrate pH 6</td>
<td>Dako</td>
</tr>
<tr>
<td>CD105</td>
<td>Rabbit, polyclonal</td>
<td>Proliferative endothelial cells</td>
<td>1:50</td>
<td>0.1 M Citrate pH 6</td>
<td>LabVision, Medicalkit</td>
</tr>
<tr>
<td>Cleaved caspase 3</td>
<td>Rabbit, polyclonal</td>
<td>Activated caspase 3</td>
<td>1:100</td>
<td>0.1 M Citrate pH 6</td>
<td>Cell Signaling, Medicalkit</td>
</tr>
<tr>
<td>GFAP</td>
<td>Rabbit, polyclonal</td>
<td>Astrocyte cytoskeleton</td>
<td>1:20 000</td>
<td>0.1 M Citrate pH 6</td>
<td>Dako</td>
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<tr>
<td>Ubiquitin</td>
<td>Rabbit, polyclonal</td>
<td>Ubiquitinated proteins</td>
<td>1:2000</td>
<td>0.1 M Citrate pH 6</td>
<td>Dako</td>
</tr>
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The primary antibodies were added and the slides were incubated overnight at 4°C. Next day, slides were washed and the signal amplified utilizing a biotinilated species-specific secondary antibody (diluted as 1:500, Dako, Medicalkit, Craiova, Romania) and an ABC HRP kit (Dako), each step with a 30 minutes incubation time. The signal was finally detected with 3,3'-diaminobenzidine (DAB) (Dako).

For the double anti-GFAP/anti-CD31 staining, as the antibodies were raised in different species, we have utilized a sequential technique, in which anti-GFAP staining was completed until chemical detection with DAB, followed by a new overnight incubation of the slides with the anti-CD31 antibody. Next day, biotin remnant from the first ABC detection was blocked by consecutive incubations with Avidin and Biotin solutions (DAKO) and then a new biotinilated species-specific secondary antibody was added. ABC AP protocol was followed and the color developed with Fast Red in the dark (Cell Signaling, Medicalkit).

For double immunofluorescence studies, the antibodies against CD31 (mouse) and CD105 (rabbit) were incubated simultaneously overnight, and the next day detected with a mix of anti-mouse Alexa Fluor 488 (Invitrogen, Medicalkit, Craiova) and anti-rabbit Alexa Fluor 596 (Invitrogen) diluted as 1:300 and incubated for one hour at room temperature.

All intermediate washing steps were done in 0.1 M PBS, pH 7.2, and all antibodies were diluted in PBS with 1% BSA (Sigma-Aldrich). Finally, the slides were cover-slipped after a light Hematoxylin staining using either glycerol (Dako) for the double immunostainings, or DPX (Fluka, Medicalkit) for all the other chemically-detected slides. For the fluorescence study, the sections were counterstained with DAPI and then coverslipped with an anti-fading medium (Dako).

Control slides were utilized for all immunostaining procedures, an age-matched control for general normal reactivity, a fragment of placenta for CD105 staining, and a confirmed Alzheimer’s disease case for anti-Aβ, tau, ubiquitin ant activated caspase 3 stainings.

Lastly, the sections were imaged with a Nikon 90i microscope (Nikon, Apidrag, Bucharest, Romania) equipped for fluorescence; with a 5-megapixel CCD camera, and images were grabbed with apochromatic objectives, as uncompressed TIF files utilizing the NIS Elements BR software (Nikon).

Immunohistochemical description

Reactive astrocytes identified on Hematoxylin–Eosin as the glial scar were heavily overexpressing GFAP. Areas of diffuse astrogliosis surrounded cavitation lesions while an alternance of focal/diffuse gliosis could be identified farther, around the lesional sites. As a general feature in all the other neocortical areas, intense GFAP reactivity was present with a bi-laminar appearance, in the subpial glia limitans and at the border between white-gray matter (Figure 4, A and B). Gliosis was also present in hippocampus, striatal nuclei and thalamus, and to a lesser extent in subcortical nuclei and brainstem.

In the more recent liquefactive lesions, and coating the cavities of older lesions, foamy macrophages were readily identified as CD68 immunoreactive (Figure 4C). In distant regions and contralateral sites, resident or migrated activated microglia were also CD68 positive, typically located around blood vessels, and had blunt, retracted extensions (Figure 4D).

Anti-ubiquitin staining identified numerous dystrophic neurites as a dotted pattern in the white matter, an aspect recognized as normal with aging, together with the plethora of corpora amylacea described earlier. In the neocortex, however, a few dying neurons appear surrounded by these ubiquitinated neurites, although a staining for activated caspase 3 did not show any apoptotic nuclei on serial sections (Figure 4E). A further staining for abnormally phosphorilated tau protein (at Serine 202 and Threonine 205, recognized by the AT8 antibody) revealed only very rare neurophil threads in the gray matter but no tangles (Figure 4F). No amyloid plaques or cerebral amyloid angiopathy could be identified after the anti-Aβ staining (data not shown).
Except for foamy macrophages or debris, the only other element remaining in the liquefaction and cystic cavitation areas were the blood vessels and immunostainings against CD31 showed the persistence of endothelial lining for most of these vessels in the inner core of the lesion (Figure 5, A and B). Only in older cavities, endothelium staining had a discontinuous appearance. Moreover, none of the vessels situated in the necrotic regions show signs of erythrocyte extravasation, compared to petechial hemorrhages in regions isolated from the liquefaction areas (pontine areas, as described before).

While astrocytes were present to form the gliotic scar in the perilesional sites, and abutted on the abluminal sites of the vessel lumens, we could not observe any astroglial cells surrounding the vessels surviving in the liquefaction areas. In order to better describe this observation, we performed a double immunostaining for vessels (anti-CD31) and astrocytes (anti-GFAP). Indeed, the glial scar lining the necrotic area did not extent any astrocytic components in the lesion although vascular elements were still present inside (Figure 5C). Some of these vessels had an angiogenic profile (as stained only for CD105), others
were more mature (stained for both CD31 and CD105) or exhibited a completely differentiated phenotype (CD31 only) (Figure 5D). Astrocytes in the scar had wide contacts with the vascular walls, and with a clear-cut demarcation, no astroglia abutted the lesional vessels. This observation was valid for both white and gray matter and for cortical and subcortical regions. In the distant perilesional areas, a qualitative inspection showed that astrocytes had much less contact surface area with the abluminal side of the vessels, and when we stained a section from an age-matched control patient, there was almost no reactivity for GFAP in the same anatomical regions (Figure 5, E and F). Thus, the reactive looking-like astrocytes in the perilesional sites seemed to increase the contact areas with the vascular walls; compared to fibrous-like astrocytes with clearly less contact area in the distant affected regions; & with the normal astrocytes, which expressed almost no GFAP around the vessels.

Figure 5 – Double immunohistochemistry for blood vessels (CD31 – red) and astrocytes (GFAP – brown): (A) Persistent blood vessels in a liquefied region with no GFAP-positive astrocytes around them; (B) Blood vessels persisting in a cystic cavity, although the endothelium look rather discontinuous in some of them (arrows), astrocytes are present only in the adjacent scar region (lower part of the image); (C) Clear-cut persistence of blood vessels in a cortical liquefactive site (left) with abundant astrocytic response in the scar (right); (D) Alternance of newer maturating vessels (CD105+ red and CD31+ green), as CD105 persists focally (arrows), with mature vessels (CD31+ only) at the arrowhead – infarct region; (E) GFAP astrocytes abutting blood vessels in a peri-lesional cortical region, while in a control cortical slide (F) astrocytes barely express GFAP. Scale bars represent 50 µm.
Discussion

Patients suffering from massive hemispheric ischemic strokes are considered at high risk for developing brain edema and therefore today much of the therapeutic efforts are concentrated around restoring blood vessels’ permeability and controlling edema [9]. However, hemorrhagic transformation is another complication that has to be considered when administering an anti-coagulant therapy [10–14].

The pathology of ischemic stroke can be subdivided into three major events: acute neuronal lesion (from the appearance of the first anoxic neurons at approximately 4–8 hours, until the apparition of gemistocytes around 36–72 hours); organization phase (with the occurrence of foamy macrophages in the first days post-stroke, to a few months – with the formation of the cystic cavity and the glial scar); and resorption phase (with the persistence of a cystic cavity surrounded by gemistocytes, neovascularization in the absence of inflammation – from months to years) [15–17].

Cytotoxic edema is thought to appear around 12 hours after the onset, together with a loss of white-gray matter demarcation on pathological inspection. It has been showed that usually after 24 hours from the ischemic episode, due to endothelial hypoxia and reflux from neighboring regions, petechial hemorrhages may occur [4, 18, 19]. Extravasated red blood cells do not survive more than a few days in the parenchyma, initially due to depletion of their energetic reserves, complement activation, and macrophage activity later on [20]. The presence of intraparenchymal migrated erythrocytes seems to be responsible for a second wave of edema developing around the 2nd to 3rd week from the clinical onset. Neo-vascularisation has been described to occur adjacent to necrotic areas and in the penumbra as endothelial cells start to proliferate as early as 12–24 hours after the injury [21–24], and active angiogenesis takes place from days 3–4 [25]. Edema might arise too from these new abnormally leaking blood vessels, and more, this could also be the source of secondary hemorrhagic strokes after ischemic lesions.

An asymptomatic hemorrhagic event of infarction is a relatively frequent event, generally not linked to anti-coagulant therapy, and not always considered to modulate the functional outcome of the disease [3], unless it occurs in a vital region in the brain. Only a few cases have been described in the literature that present simultaneous hemorrhagic and ischemic strokes, and even fewer that present a hemorrhagic lesion occurring after an older ischemic stroke, and in a distant anatomical region [26–28]. The factors that govern this phenomenon are largely unknown [4].

What captured our attention was the fact that none of the cortical ischemic lesions presented any hemorrhagic transformation, and the fact that at the time brain imaging were performed, no lesion had been detected in brainstem. Therefore, it must have been that the pontine hemorrhage was recent, and due to its location, most probably was the cause of death. During the anti-coagulant therapy administrated in the hospital, coagulation status was normal, and together with the steady symptomatology, there was no suspicion of possible bleeding. No clinical sign or symptom predicted the onset of the hemorrhage except the rapid installation of a comatose state and exitus. Pathological examination found no apparent brainstem vascular malformation to give a direct explanation for the hemorrhagic event in this area and no vascular amyloid angiopathy was found [29]. Vascular hyalinization was indeed observed, but only to a lesser extent, and only in the telencephalon.

Altogether, there was no anatomical or gross pathological explanation for the timing of this acute event, considering that the patient had survived with massive ischemic lesions in the anterior and middle brain regions. There were no recordings of any familial neurological diseases, and if a hypertensive state determined the hemorrhage, why did this not occurred in the already suffering blood vessels from within the ischemic core or its penumbra? Could it be that blood vessels were somehow more protected against red blood cells extravasations, albeit suffering, around the ischemic lesion sites? For example, VEGF-A, agiopoietin 1 and estrogens are only a few mediators proved also to protect existing endothelial cells [30–32].

Although primary pontine hemorrhage accounts for less than 8% of the total brain hemorrhages [33, 34], it is associated with a much higher mortality rate due to the pontine localization of cardiovascular centers as well as the numerous ascending and descending pathways [33]. As in our case, brainstem hemorrhagic strokes are characterized by a rapid onset coma and rapid exitus rather than just motor deficits. Although brainstem ischemic strokes are also not frequent (compared to diencephalic and telencephalic localizations), localized pontine ischemic strokes evolve commonly with sensory and motor deficits and less frequently as life-threatening events [35]. In both cases, if the patient survives long enough, pathology evolves as in any other brain ischemic lesion [15].

It is a well known fact that hypoxia induces an increased permeability and breakdown of blood brain barrier in cerebral ischemic diseases [36–38]. Endothelial cells have been proved themselves an important source of free radicals under hypoxic [6, 7] and mechanic stress conditions [39], but on the overall it seems that they are more resistant to such factors compared to neurons and glial cells [39]. On the other hand, in has been also demonstrated that hypoxia induces a loss of endothelial cells and astrocyte integrin receptors, explaining in part the missing glia limitans around these affected vessels [40, 41].

Apart from being able to survive longer in hypoxic conditions, even considering an intact blood flow through
these vessels after tissue necrosis, many proteases, vasoactive signals [24], and inflammatory cytokines have been proved to be released from necrotic brain parenchyma and should affect in the end blood vessels’ integrity [42].

Our report also identified remnant as well as newly formed blood vessels in the liquefaction areas and even in old cystic lesions, completely devoid of any astrocytic support as we might have expected. It is known that astrocytes are generally more resistant to hypoxia compared to neurons [5], and the present study confirms that in fact endothelial cells are even more resistant than astrocytes [6, 7].

As it has been showed that astrocytes inhibit increasing permeability of blood brain barrier during hypoxia [8], it would seem that the vessels in these particular regions do not show much protection to this factor in infarct regions as no astrocytes were present around them. Indeed, when we studied a slide from a control patient, minimal astrogliosis was detected around blood vessels compared to the presence of GFAP laden glia in distant ischemic regions, suggesting their protective role in the latter case. Different astrocytic functional and morphological responses have been reported considering the areas of the brain from which they originate [5, 43, 44], but in this case, both gray and white matter, cortical or subcortical astrocytes were missing in the lesional areas.

It remains to be addressed to what mechanisms extent protection to these glia-deviated vessels in the ischemic core or penumbra, as possible therapeutic targets against brain hemorrhages. This it would be of interest to gather and study more cases of distant hemorrhagic events after older ischemic strokes in order to find common pathological denominators.

Conclusions

The conclusion of this report is twofold. First, although minor, the acute hemorrhagic transformation areas found in the brain stem most probable associate as death precipitating events in this patient surviving after massive ischemic lesions in telencephalon and diencephalon. On the other hand, variable resistance of vascular endothelium to ischemia is an important factor to consider in preventing secondary localized bleedings after an ischemic stroke, and further on, when discussing future treatment options.

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