Cryptic fibromuscular dysplasia in the meningeal vessels. An autopsy study

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Abstract

We retrospectively evaluate the presence of cryptic fibromuscular dysplasia (FMD) (*i.e.* not macroscopically visible and not associated to FMD in larger arteries) in the small meningeal vessels in a comprehensive series of patients. Such a study has not been performed before to our knowledge. The meningeal tissue has been systematically examined in a series of 100 consecutive autopsies. The immunohistochemical study was performed in one case with leptomeningeal FMD. In the whole series only one case had FMD in the small leptomenigeal arteries. The histological variant was intimal fibroplasia, a rare variant of FMD. Immunohistochemistry was necessary to confirm this peculiar change of the vascular wall. Cryptic fibromuscular dysplasia in the meninges is a very rare finding in our series of autopsied patients – 1% of cases, in concordance with the literature data. The clinical associations of this lesion are difficult to be related to this lesion. A cryptic presence of FMD must be suspicioned in some cases with stroke.

Keywords: fibromuscular dysplasia, cryptic, meninges, autopsy, immunohistochemistry.

Introduction

Fibromuscular dysplasia (FMD) is a nonatheromatous disease of small to medium-sized arteries [1], although cases with vessels of all size being involved have been described [2].

It was firstly recognized as a distinct entity in 1938 [3, 4]. Several forms of histopathologic FMD are described: intimal fibroplasia, medial fibromuscular dysplasia and periarterial fibroplasia [5, 6].

Of these, the medial arterial layer is most frequently involved; on the other side, the intimal fibroplasia is one of the rare. We did not find systematic immunohistochemical studies regarding this latter variant.

Only recently the involvement of this entity in the pathology of the nervous system has been described, with a frequency of about 25–30% of patients [7, 8]. Usually, a cervicocranial disposition is seen in most cases, especially the extra-cranial segments of the internal carotid and vertebral arteries.

A cryptic localization of FMD only within the small arteries of the leptomeninges, sparing the brain parenchyma as well as the medium-sized cranial vessels is not described to date to our knowledge; therefore we decided to perform such a study in a series of 100 consecutive autopsies.

The cervicocranial FMD is commonly associated with hemorrhagic or ischemic events in the brain [9], mainly related to the dissection or aneurisms of the internal carotid and basilar arteries [10].

In our study, however, the histopatologic evidence of cryptic FMD features in only one case was associated to multiple strokes. In our series we found FMD – the intimal fibroplasia variant – only in one case, fact that is in accord with the relative frequency in the literature.

We emphasize on the pathologic features, consider the differential diagnosis, and immunohistochemical investigation of the lesion.

Material and methods

The entire leptomeninges over the cerebral hemispheres was collected, in a series of 100 consecutive autopsies. None of the cases showed macroscopic features of stenoses or dilatations of the arteries of the circle of Willis. The leptomeninges also were normal at macroscopical examination. The age of patients varied between 48 and 90 years (mean 71.56), 46 males and 54 females. Of these, 53 had ischemic and 30 hemorrhagic strokes.

The remaining 17 cases were hospitalised and eventually died from other pathologies related to the involvement of the nervous system but without local vascular events: cerebral metastases with raised intracranial pressure, myocardial infarct with subsequent coma, digestive haemorrhage with acute hypotension, encephalitis. 58% had arterial hypertension and 6 had diabetes mellitus.

The samples were fixed in buffered formalin, included in paraffin and sectioned at 5 μm. Usual staining – Hematoxylin & Eosin and Masson's trichrome were used. Multiple sections of leptomeninges have been examined in each case.

In the only case, which disclosed the features of FMD, the immunohistochemical examination has been performed, with antibodies directed against smooth muscle actin (Sigma, dilution 1 : 1500), CD34 antigen (*Immunotech*, dilution 1 : 100) and CD68 antigen (*Dako*, *Glostrup*, *Denmark*, dilution 1 : 50).

Results and discussions

In the whole series the macroscopic examination did not reveal any features of fibromuscular dysplasia at

leptomeningeal level nor in the arteries of the circle of Willis. The microscopic examination of the vascular leptomeningeal tree showed only fibrosis, hyaline changes, and microatheroma of the small arteries. In only one case, a 78 years old man, some arteries presented changes suggestive for fibromuscular dysplasia.

The patient was hypertensive, diabetic (type II diabetes mellitus) and a smoker. In his medical records several ischemic strokes were noted. A CT examination showed cortical atrophy of the brain and a large old infarct with cystic transformation in the right occipital lobe (Figure 1). Since the patient's pathology was known, a usual small vessel disease was the most probable diagnosis and no angiographic examination has been performed.

Histopathologic findings

Most of the small leptomeningeal arteries show only diffuse sclerosis. However, some arterial profiles have peculiar changes suggestive for a fibromuscular dysplasia.

These consist of a major thickening of the intimal layer, which is composed of proliferated cells with elongated nuclei, densely packed and concentrically disposed on several layers, and occasionally surrounded by loose connective tissue. In few of these arteries a clear space between this proliferation and the preserved elastic lamina is striking (Figure 2, a and b).

This space can be considered as an incipient dissection of the wall. The medial and adventitial layers are either thinned or normal. Consequently, where these aspects were conspicuous, an immuno-histochemical examination has been performed, which show: a strong positivity for smooth muscle actin in the whole thickened proliferated intimal layer (Figure 3).

The CD34 endothelial marker labels only the normal preserved endothelium, and the CD68 macrophage marker lacks in the proliferated zones (not shown). Only few scattered smooth muscle cells are visible in the thinned media, separated by intermingled connective tissue (Figure 4).

The vessels in the adjacent brain parenchyma do not show any involvement of FMD type, with only a normal expression of the CD34 antibody in the local capillaries.

Fibromuscular dysplasia is an uncommon disease of the arterial, mainly medium and small size arteries. In the intracranial vessels it is described mostly in the internal carotid and basilar arteries. The clinical consequences may be various: from minor symptoms as headache, tinnitus or syncope [1, 7, 11] to isolated or recurrent ischemic strokes [9, 12, 13].

Regarding the pathogenesis of this condition, cigarette smoking and arterial hypertension has been associated with it, as well as some genetic abnormalities, even though the studies focused mainly at the renal localization of the lesion [14, 15]. Some abnormalities in the alpha-1 antitrypsin phenotype were also be involved in the development of FMD of the internal carotid artery [16].

FMD is thought to be a principal cause of stroke in young patients, mostly related to the cervicocranial middle-sized arteries and their dissection as a consequence [9, 12, 13].

However, the mean age for FMD disclosure in the cerebrovascular territory is 50 years [14].

The presence and evolution of the intimal type of FMD in this territory is not fully described to date. Moreover, a comprehensive study affirms that if angiographic diagnosis of FMD is frequent, histopathologic confirmation is rare [17]; therefore, the frequency of FMD of the carotid artery in a series of 20 244 consecutive autopsies was only 0.02%.

On the other hand, no studies of the presence of cryptic FMD at leptomeningeal have been done to date to our knowledge. The association of its presence in the meninges with some brain lesions is a possible theme for further careful studies.

We found in this series of 100 consecutive autopsied cases only one case with features of FMD, the intimal fibroplasia type. This variant is considered as a rare one, discovered in only 10% of cases with renal FMD [5, 6].

Our study demonstrates for the first time that FMD can be found only in the leptomeninges, without larger arteries involvement. Nevertheless, the frequency of cryptic FMD lesions in the leptomeninges is in accord to the general data in the literature regarding the forms located on the larger arteries and detected by imagery studies.

The immunohistochemical approach enabled us to confirm that the intimal fibroplasia is composed of smooth muscle cell proliferation. No contribution of the endothelial cells (CD34 was negative) as well as the macrophage component can be demonstrated (CD68 negativity) in the thickened intima.

This allows differentiating it from microatheroma. In the latter, even though the lesion is intimal, the histology must comprise foamy cells, T-lymphocytes, macrophages and a dense connective tissue matrix aside some smooth muscle cells [18]. The absence of any inflamatory infiltrate does not sustain also a possible differential diagnosis with any form of vasculitis.

The global histologic aspect could even induce the idea of some recanalised small vascular lumina, after a previous trombotic event. First, in our case no atrial fibrillation is to be noted in the medical records of the patient. Second, the lesion is too regular in shape and appears even in apparently normal vessel, as regarding the rest of the structures.

The two vessels in Figure 2 (a and b) have a conspicuous regular proliferation of smooth muscle cells within the intima, which prove to be positive to smooth muscle actin in several arteries, even with otherwise normal features (Figure 3).

The histological aspect is far from a repermeabilized vessel, which would be more irregular in shape, composed mostly of connective tissue and endothelial proliferation with chaotic arrangement of the new lumina.

Smooth muscle cells participate only in small number at this latter process. The clear space beneath the elastic lamina has some area filled with red blood cells, and also some hemosiderin deposits in the connective tissue adjacent to the proliferating cells.

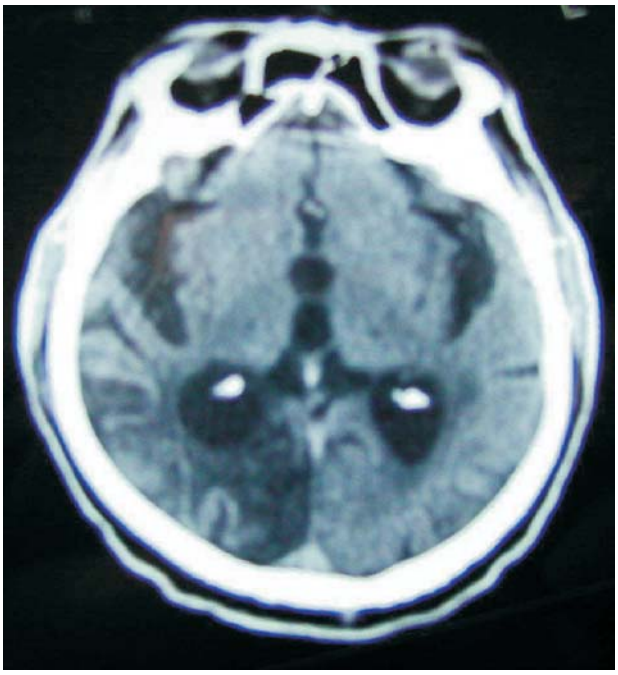
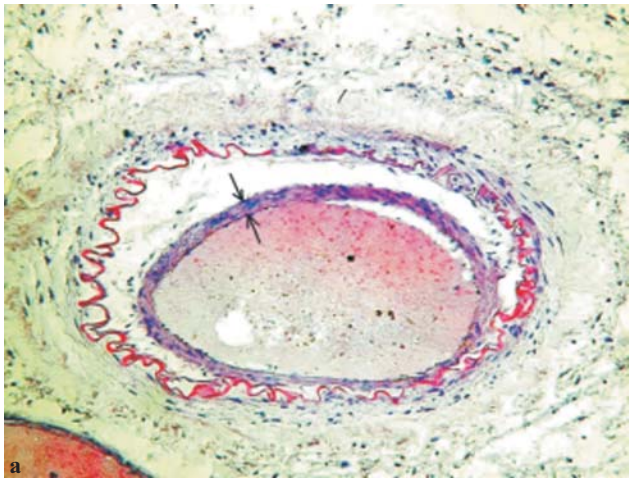


Figure 1 – *A CT-scan shows global cortical atrophy, as well as an old infarct in the right occipital lobe*



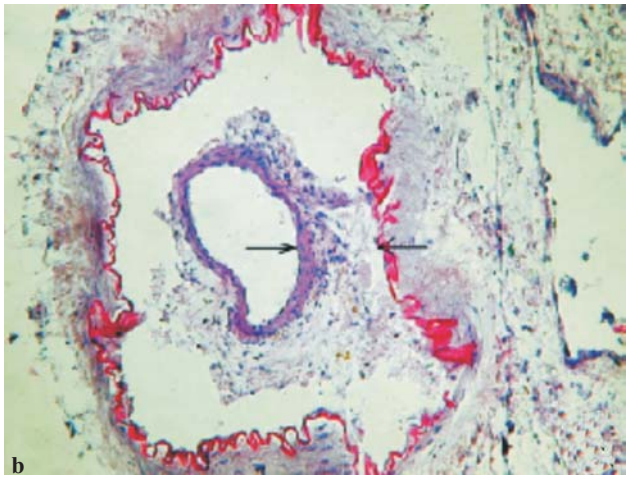


Figure 2 – **a)** *General picture of intimal fibroplasia. A 500-µm artery shows a marked proliferation of the intimal layer. The elastic lamina is normal and a certain fibrous thickening of the adventitia;* **b)** *Also in a large artery, around the cellular proliferation an area of fibrous loose connective tissue is conspicuous. A large, clear space is visible in both figures between the intimal proliferation and the media (HE staining)*

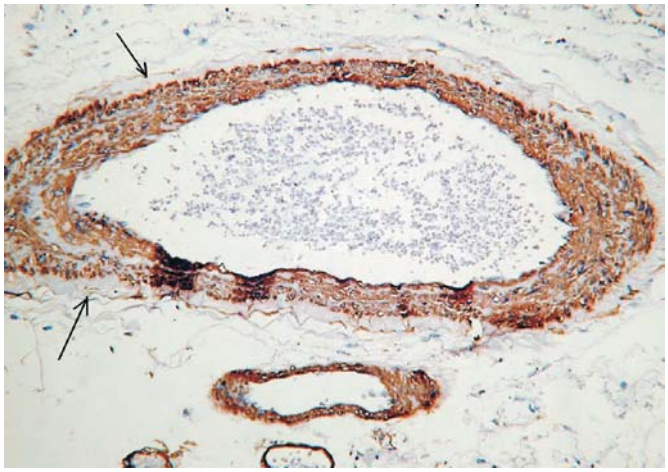


Figure 3 – *Intimal proliferation is composed of densely packed smooth muscle cells. The global structure of the arteries is preserved. Smooth muscle actin antibody*

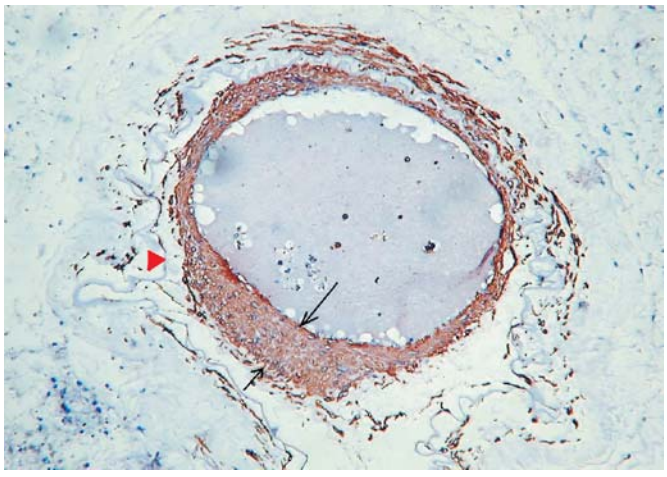


Figure 4 – *Arterial media shows only few, scattered smooth muscle cells, replaced by fibrous connective tissue. This is in contrast to the large intimal proliferation. Smooth muscle actin antibody*

This feature leads as to think to a dissection of the previously abnormal dysplastic vessels. Some small vessels show also positivity for smooth muscle actin, a phenomenon not so rare in practice.

Regarding a possible pathogenesis hypothesis, since 58% of our series had arterial hypertension and 6 had diabetes mellitus without presenting features of FMD, no valuable correlation can be done among these pathologies and this, at least in our series.

The finding of cryptic FMD features only within few arterial profiles on multiple sections, in small arteries of the leptomeninges demonstrates that it is a focal lesion and it should be carefully assessed in patients with multiple strokes in their history. Angiography could be performed, but its role in the identification of lesions in such small vessels is difficult to assess.

A connection between this type of scattered lesions and the subsequent multiple infarcts in antecedents have to be confirmed in further studies. In our series this was only one case, associating multiple brain infarcts in his antecedents.

Obstruction by dissection of some perforant arteries with FMD could be considered as one possible mechanism. The early detection of such cryptic FMD localization can determine some stroke preventing therapy, even though percutaneous angioplasty, commonly effective as curative in renal localizations is not possible for small vessels as those in the leptomeninges. However, antiplatelet agents can be used in such patients if a prompt detection of this uncommon lesion is done [19, 20].

Conclusions

Cryptic fibromuscular dysplasia in the meninges is a very rare finding in our series of autopsied patients – 1% of cases, in concordance with the literature data.

The clinical associations of this lesion are difficult to be related to this lesion. A cryptic presence of FMD must be suspicioned in some cases with stroke.

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