Intraspinal Aneurysm In Primary Sjögren's Syndrome And Cryoglobulinemia Type II, “In-Vivo Model” For Aneurysm Genesis And Regression.

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Citation

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Abstract

A patient is presented with aneurysmal SAH with primary Sjögren’s syndrome who had an infrequently-reported vasculitis and cryoglobulinemia due to a monoclonal IgM (kappa) paraprotein with rheumatoid factor activity. The conservatively-treated aneurysm showed spontaneous regression. The literature regarding the rare pathology is reviewed. The formation and regression of this special type of aneurysm and the therapeutic implication as a possible in-vivo model for pathogenesis are discussed.

INTRODUCTION

Sjögren’s syndrome (SS) is an autoimmune exocrinopathy with highly variable systemic clinical features. Since the prognosis is generally good in patients with primary SS, there have been few autopsy reports. Vasculitis due to mixed cryoglobulinemia is a recognised feature of Sjögren’s syndrome. Vasculitis may also occur in primary SS due to hypergammaglobulinaemia in the absence of cryoglobulins. We report on a case of a patient in whom SAH H&H grade I revealed the presence of an intraspinal inflammatory aneurysm that regressed under antiinflammatory medications without invasive intervention.

CASE REPORT

A 47-year-old women initially presented with acute headache and(?) meningism in March 2007. At the time of the first presentation to our department, clinical examination revealed only positive Kernig’s sign, no motor or sensory focal deficit, so clinical suspicion of H&H grade I SAH was raised. The patient had definitive diagnosis of Sjögren's syndrome (SS) with Cryoglobulinemia Type II 15 years ago and received a course of medical treatment after this initial diagnosis, but 3 years later the patient had decided to stop medication because of conception planning.

The following laboratory results were found: The complete blood picture and plasma biochemistry were normal, ESR 210 mm/lst h, and antinuclear factor positive (titre 1/50; normal <1/40). Antibodies to extractable nuclear antigen, Ro(SSA) and La(SS-B), were positive. Rheumatoid factor was detected by both latex agglutination and by the Rose-Waaler test. Cryoglobulins (3.3 g/l) were shown by immunofixation to consist of polyclonal IgG and a monoclonal IgM kappa paraprotein (type II cryoglobulinemia). Complement showed decrease in their normal value, but was 11mg/l with C3d, HCV and HBV serology were conclusively negative. Serum creatinine level was 3 mg/dl at presentation, renal biopsy revealed MPGN type II in association with cryoglobulinemia Type II pathology. Cardiac involvement was proven in chest plain x-ray revealing an increase in cardiac shadow. CT revealed SAH located around the medulla, in cerebellomedullary and cerebello-pontine cistern, with reflux into the third ventricle (Fig 1). A 4-vessel angiography on the same day revealed bilateral constriction and irregularities of the vessel wall of both vertebral arteries at V2 level and an intraspinal small aneurysm about 2 mm parented by the very small intraspinal branch of the right vertebral artery just above the upper border of C3 (Fig 2). Due to the dangerous anatomy (proximity to ASA) and the assumed difficulty of reaching the aneurysm through the very tiny spinal branch of the vertebral artery, and also considering the benign clinical presentation, only conservative medical treatment was performed (corticosteriod (Decortin) 5mg once daily; azathioprin (Imurek 50mg) once daily;

diaminodiphenylsulfon (Dapson 50mg) twice weekly). An angiographic follow-up after 6 months was planned .Unfortunately the patient`s condition worsened regarding the extra-CNS manifestations of the collagen disease, where she developed progressive severe Reynaud's phenomenon in the upper and lower extremities . Follow-up angiogram in April 2008 revealed complete resolution of the vasculitic irregularities of the vertebral arteries and complete regression of the previously encountered intraspinal aneurysm (Fig 3). At the same time, it was obvious that serum creatinine level was lowered, indicating possible amelioration of renal pathology on medical treatment.

Figure 1

Figure 1(a,b) NECT showing SAH around the medulla and near the foramen magnum.

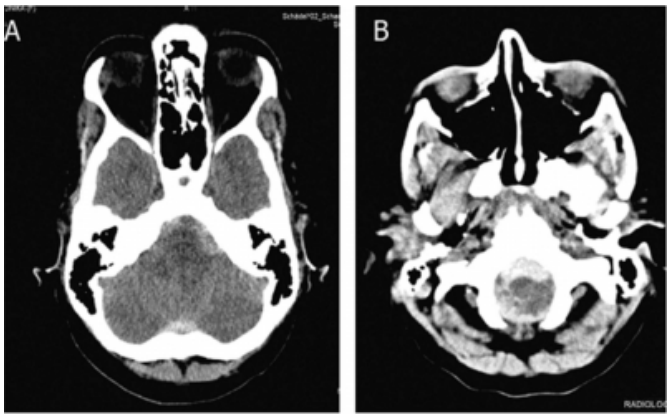


Figure 2

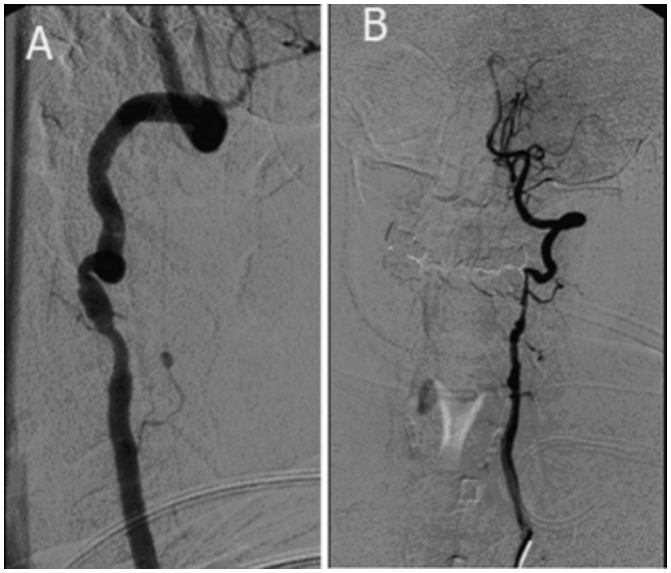
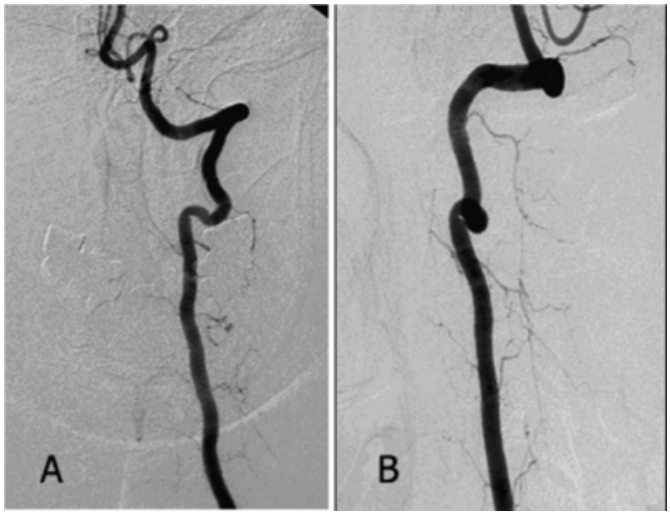


Figure 2 (a), first angiogram lateral view right vertebral artery shows a very small intraspinal aneurysm of the fifth cervical segmental artery : distal to it the vertebral artery shows severe vasculitic irregularities ,(b),AP view angiogram of the left vertebral artery shows long segment of vasculitis with vessel irregularities.

Figure 3

Figure 3(a) follow-up after 1 year. left angiogram of vertebral artery showing complete improvement of the vasculitic constriction and irregularities (b) at right vertebral angiogram shows regression of the aneurysm and complete restoration of the normal caliber of the artery.



DISCUSSION

Two distinct types of IVD have been observed: neutrophilic IVD (NIVD) and mononuclear IVD (MIVD). Molina et al. previously reported a striking association between the presence of autoantibodies to the small molecular weight ribonucleoprotein, Ro (SS-A), and rheumatoid factor and the occurrence of vasculitis [1, 2]. In that study a subgroup of SS patients with IVD who were seronegative was also reported [1]. In another study, Molina et al. further examined the histopathological and serological correlations of patients with SS who have biopsy-documented IVD. There was a statistically-significant association of NIVD with seropositivity for Ro (SS-A), rheumatoid factor, and antinuclear antibodies [12]. Hypocomplementemia occurred in the NIVD group, while patients with MIVD had normal complement levels. These observations suggested that the two histopathological types of IVD in SS may be mediated by different immunopathogenetic mechanisms. In contrast, MIVD tended to occur in the setting of seronegativity with respect to these autoantibodies, with normal complement levels. NIVD, as defined in this study, was histopathologically indistinguishable from leukocytoclastic

vasculitis or hypersensitivity vasculitis [12]. Leukocytoclastic vasculitis has previously been observed to affect predominantly postcapillary venules, although, other vessels may be less commonly involved [12].

The other histopathological type of IVD observed in SS (MIVD) is less well recognized. Few reports have been published describing the histopathological form of necrotizing arteritis in patients with Sjögren's syndrome [12, 13, 15].

It was detected that both MIVD and NIVD can produce significant alterations in blood vessel integrity. In particular, central nervous system disease, unattributable to other causes, has been observed with equal frequency in both types of IVD.

In MIVD, there is direct vessel wall invasion by mononuclear inflammatory cells with alteration/destruction of the normal architecture of the vessel wall. There are hyperplasia and hypertrophy of endothelial and smooth muscle cells and, in some cases, vessel lumen occlusion. Elastin-containing vessels show disruption of the internal and external laminae. Fibrin deposit and erythrocyte extravasation, although present in some cases, are not necessarily required for significant alteration of vascular integrity. Furthermore, repeated biopsies of lesions of varying age in the same individual over time have consistently revealed the continued presence of MIVD (except in cases where a transition from MlVD to NIVD occurred)[12].

Cryoglobulins are immunoglobulins that precipitate from serum at temperatures below 37ºC[6, 16]. The level of cryoglobulinemia does not always correlate with the level of symptomatology [7].

Three types of cryoglobulins have been identified. We focus our discussion on type II cryoglobulinemia, the most frequent variant and the type involved in our patient.

Mixed cryoglobulinemia type II consists of a mix of IgM and IgG proteins that resemble classic rheumatoid factor [11]. Therefore, mixed type II is associated with elevated rheumatoid factor.

Mixed cryoglobulinemia is associated with autoimmune diseases and chronic inflammatory, immunoproliferative, and infectious diseases. Renal and neurologic involvement is more frequent in type II [4].

There is very large association between type II cryoglobulinemia and hepatitis C virus[9], but this was not the case in our patient.

In type I cryoglobulinemia, there is direct obstruction of vessels, in contrast to types II and type III, which cause systemic vasculitis secondary to inflammation of the vessel walls induced by the deposit of IgM-IgG complexes and activation of complement [6]. Leukoclastic vasculitis occurs with fibrinoid necrosis and thickening of the vessel wall and inflammatory infiltrate consisting of neutrophils, as well as destruction of neutrophils, nuclear dust, and neutrophilic debris.

The patient we describe has primary SS complicated by vasculitis and cryoglobulinemia with an IgM kappa paraproteinaemia.

At this point, we can postulate that our case represents vasculitis-induced aneurysm due to the presence of two different pathological mechanisms; one is the Sjögern syndrome , and the other is the pathological effect of cryoglobulinemia type II.

Based on the serological and pathological data of this patient, the type of vasculitis encountered was (NIVD) type, and this is in agreement with the findings of Molina et al.

Molina et al. didn`t report any difference between the two types of vasculitis regarding clinical severity of the disease. However, we can propose that the impact of the NIVD pathological process is more severe than that of the MIVD, especially in producing the rarifying ischemia in the vessel wall. This may be the explanation of the aneurysm genesis in our case.

Considering that the other pathological factor can be related to the presence of cryoglobulinemia type II, in which this pathological process can be more responsible for the cellular infiltrative changes of the vessel wall and the vessel wall thickening changes by macromolecule depositis. we may contribute the presence of constriction of the vertebral arteries in our patient to this effect.

The coincidence of both actuating pathological processes at same time, the presence of vessel wall weakening effect by the NIVD and infiltrative- constricting effect due to cryoglobulinemia type II, may provide an in-vivo model for aneurysm formation due to high flow shear stress, local pressure related to the constriction and expressed on a very

weak vessel wall point due to NIVD pathology. Unfortunately, we did not have the possibility of testing our postulation by dynamics-related study.

On the other hand, the good response to medical treatment in our case may further support our speculation. Due to the good pharmacological response of the cryoglobulinemia II vascular pathology, the chance was given in the sense of the in-vivo model proposed above to eliminate the constriction as one of the contributing pathologies. So amelioration of the flow reflux pressure inside the aneurysm occurred, and led sequentially to the formation of the thrombosis.

But considering the good outcome and better treatment response for cryglobenimia type II-associated vasculitis in some studies compared to that of primary SS vasculitis, we may relate the improvement that occurred in our patient to the better response of the cryoglobulinemia pathology to the restarted medication after the discovery of the aneurysm.However, isolated spinal artery aneurysms are rare, and few cases have been reported [14, 17] . Spinal artery aneurysms associated with arteriovenous malformations are more numerous [5]. Spinal artery aneurysms may also be associated with other entities that increase hemodynamic stress, such as aortic coarctation or bilateral vertebral occlusion in cases in which the spinal artery circulation is recruited as the collateral pathway [8].

Massand et al. reported 4 cases of intraspinal aneurysms. Mostly they were located in the lower thoracic or lumbar regions. Histopathologically, two of them were resected and were classified as dissecting aneurysms. Depending on the histopathological findings, the author adopted a more invasive approach for treating such type of aneurysms [10].At our center, Berlis et al. previously reported three cases with intraspinal aneurysms, one was serologically proven to be infectious in aetiology. All were in lumbar or lower thoracic segments. Because of a "wait and see " strategy and spontaneous regression of these aneurysms, no histopathological biopsy was performed[3] .

We can not elucidate a systematic paradigm for the treatment of this very rare syndrome by reviewing previously-reported cases, since in most cases a histopathological biopsy was not available. But either removal of the incriminated pathological promoter or interventional treatment of the aneurysm both sound logical. The selection depends on the data available regarding the pathogenesis of the aneurysm and the benignity of its course. All these data should be available if we are to design such a therapeutic plan. The proposed reflexive behaviour toward the invasive approach usually adopted in such situations was restrained in the before-mentioned cases . Therefore, it was important to observe that spontaneous regression is also possible in some situations. In our case, the pathological promoter could be removed with medication, leading the aneurysm to regress spontaneously .

CONCLUSION

We now have an increasing number of published aneurysm with spontaneous regression after conservative treatment and, this case shows the dual effect of constricting and weakening pathology on the formation and thrombosis of an aneurysm due to concurrence of Sjögren's syndrome and cryoglobulinemia type II. It may be with some others; a basis for an in-vitro model design by which we can study the pathogenesis, hemodynamic changes and therapies for such aneurysms

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