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Additional triggers of endothelial dysfunction modulate antiphospholipid-mediated microangiopathy in a central nervous system-cutaneous syndrome

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ABSTRACT

It is now recognised that the spectrum of antiphospholipid (aPL)-mediated syndromes includes end-organ injury due to microangiopathic manifestations. In the central nervous system (CNS), the clinical and radiographic appearance of microangiopathic lesions can be notoriously difficult to distinguish from multiple sclerosis (MS). A patient is presented who developed white-matter lesions in the brain and spinal-cord, shortly after receiving toxic doses of radiation for an arterio-venous malformation. The institution of interferon therapy for presumptive MS not only led to worsening neurologic deficits, but triggered a cutaneous syndrome with pleomorphic stigmata of microvascular injury (livedo reticularis rash, splinter haemorrhages). Subsequent workup revealed persistently elevated high-titer antiphospholipid of multiple isotypes. Treatment with corticosteroids and immunosuppressant therapy afforded improvement in locomotor function. We hypothesise that radiation injury and treatment with interferon-therapy constituted iatrogenic "hits" of endothelial injury, and potentiated aPL-mediated microangiopathic disease affecting the CNS and the skin.

Introduction

Antiphospholipid antibody (aPL) syndrome is a systemic autoimmune disorder, with thrombophilic events mediated by pathogenic phospholipid-binding antibodies (1-2). Although the larger-vessel thrombotic episodes occurring in aPL syndrome may be acute and fulminant, the microangiopathic manifestations of aPL syndrome may be more subtle and indolently progressive (3).

In this report, a patient is presented who developed spinal cord and brainstem lesions misconstrued as MS shortly after receiving toxic doses of radiation for a ruptured arterio-venous malformation (AVM). In the context of receiving beta-interferon treatment for presumed MS, she developed pleomorphic skin lesions indicative of microangiopathic disease, including splinter haemorrhages, abnormal nailfold capillaries, and livedo reticularis rash. She also developed worsening spastic paraparesis. The evaluation revealed serial, high-titer aPL antibodies, as well as serial hypocomplementemia.

This case is notable in several respects. The patient's dramatic evolution of CNS and cutaneous lesions remarkably parallels several experimental models, in which sequential triggers of endothelial dysfunction are required to cause aPL-mediated small-vessel disease. It is hypothesised that whereas the history of radiation toxicity likely constituted a "second hit", the institution of beta-interferon therapy – with polarisation towards a TH2-biased cytokine milieu – then led to a permissive environment culminating in aPL-mediated CNS and cutaneous disease. This report represents the first example in the literature of beta-interferon therapy not only associated with worsening aPL-mediated neurological disease, but causing graduation of a regional CNS syndrome to a systemic syndrome characterised by pleomorphic, microangiopathic skin lesions. The role of complement activation in propagating this patient's cutaneous and CNS syndrome is discussed.

Case report

A 54-year-old right-handed female, with a history of a ruptured left arterio-venous malformation (AVM) with resulting left intraparenchymal haemorrhage, was referred to the Johns Hopkins Neuro-Rheumatology Clinic, for evaluation of diplopia, deterioration of gait, and rash.

In the early 1980s, the patient developed headaches and right-sided focal motor seizures. MRI of the brain revealed a large left temporal-parietal AVM. In the early 1990s, despite two platinum-coil embolisations, the patient developed worsening right-sided focal symptoms related to left cortical dysfunction: she had right homonymous hemianopsia, and spastic right-sided weakness. In 1993, she underwent an experimental protocol of Bragg-Peak proton radiation therapy. In the following weeks, she developed acute radiation toxicity, characterised by nausea and vomiting, alopecia, and bilateral sensorineural hearing loss.

From 1993 to 1995, she developed new symptoms and signs, related to cervical

spine disease. She experienced Lhermitte's phenomenon, or sensations of electric shocks down both legs, upon flexion of the neck. Examination revealed spastic paraparesis of both lower extremities (Medical Research Council [MRC] of 4/5 in proximal muscles in right lower extremity [LE], and 4 to 4+/5 in left lower extremity) (4). In 1995, she suffered acute intraparenchymal haemorrhage of the AVM, and was left with residual Broca's aphasia. In 1995, the entire margins of the AVM were surgically extirpated.

From 1995 to 1996, she developed diplopia, and MRI reportedly revealed new lesions in the dorsal brainstem, remote from the region of the left AVM. Given that she had clinical and radiographic evidence of disseminated lesions in the brainstem and cervical spinal cord, she was given a tentative diagnosis of MS. At this point, no treatment was offered.

A comprehensive review of systems did not suggest the presence of any systemic rheumatic disease: there were no headaches, oral ulcers, shortness of breath or symptoms of serositis, haematuria, joint pains, or sicca symptoms. Repeated lumbar punctures did not reveal any pleocytosis, had normal glucose and total protein, with no oligoclonal bands and a normal IgG synthetic rate.

From 1996 to 2004, she suffered worsening spastic paraparesis and diplopia. In 2000, MRI reportedly revealed non-enhancing, multifocal lesions in the cervical spine. In winter, 2004, she was started on treatment with the beta-interferon, interferon-beta-1a (Avonex), at 30mg intramuscularly (IM) every week. In the ensuing months after starting interferon therapy, her husband noticed emergence of a reticular rash over the lower extremities. In 2005, the patient first had serological evaluation for antiphospholipid antibodies, revealing high-titer positivity of anticardiolipin IgM antibodies (101 MPL, normal<10), and medium-titer positivity of beta-2-glycoprotein IgM antibodies (46 STD, normal<10). Examination of other isotypes and aPL antibodies were unremarkable. She had never been pregnant.

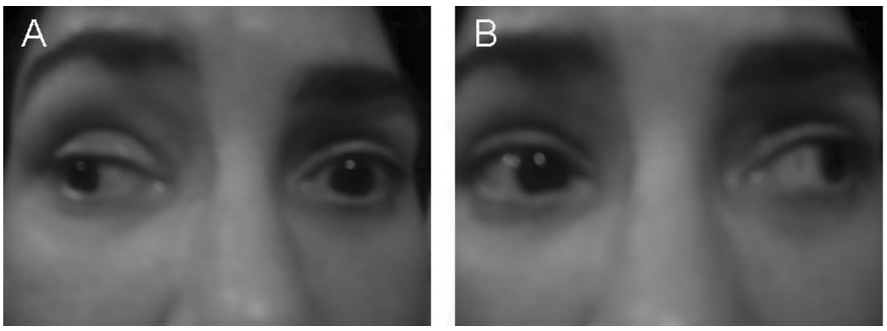

Fig. 1. Example of bilateral internuclear opthalmoplegia (INO) causing diplopia. A) Upon attempted conjugate gaze to the right, the *left* eye does not fully adduct to the midline, and is termed a *left* INO. The right eye demonstrated sustained right-beating nystagmus. B) Upon attempted conjugate gaze to the left, the *right* eye does not fully adduct to the midline, and is termed a *right* INO. The left eye demonstrated sustained left-beating nystagmus.

Also within months after starting interferon therapy, she suffered significant clinical and functional decline. Serial neurological exams documented that antigravity strength in the lower extremities was barely preserved (MRC of 3/5). Whereas, before interferon-beta-1a treatment she was able to walk up to 50 feet with a cane, by 2005, she was unable to transfer independently, and was dependent on a walker for walking minimal distances.

Because of this clinical and functional deterioration, her neurologist prescribed dexamethosone, to be administered 4 milligrams orally, every Monday, Wednesday, and Friday. Within 12 to 24 hours after oral dexamthosone dosing, the patient was able to initiate independent transfers, and was able to walk approximately 10 feet with a cane. However, such improvement waned after 24 hours. She was therefore referred for further evaluation.

Examination revealed a fatigued-appearing woman, appearing older than stated age. On neurological examination, she had diplopia because of the finding of bilateral internuclear ophthalmoplegia (INO) (Fig. 1). On motor exam, she had spastic paraparesis, with the weakest muscles in the proximal lower-extremity musculature having barely preserved antigravity strength (MRC power 3/5). Reflexes were brisker in the lower (3+) than upper extremities (3), with generalised right-reflex preponderance, and plantar stimulation induced bilateral Babinski responses. General physical examination was notable for a livedo reticularis rash on the lower extremities, splinter haemorrhages, with nailfold capillaroscopy revealing corkscrewing capillaries, along with capillary loop dropout.

Repeat serologies confirmed high-titer anticardiolipin IgM antibodies (113 MPL, normal<10), medium-titer beta-2-glycoprotein antibodies (33 STD, normal<10). She also had hypocomplementemia, with C3 of 70 mg/dL (normal 79-152 mg/dL), and C4 of 4mg/dL (normal 12-42 mg/dL). The lupus anticoagulant as assessed by RVVT was normal; other aPL isotypes were also normal. Other repeat serologies, including antinuclear antibodies (ANA), anti-double strand DNA (dsDNA), extractable nuclear antigens, rheumatoid factor (RF), anti-neutroplic cytoplasmic antibodies (ANCAs), cryoglobulins, and erythrocyte sedimentation rate were unremarkable.

Brain MRI confirmed lesions remote from the region of AVM encephalomalacia. In addition to lesions noted in the dorsal brainstem (Fig. 2A), brain MRI revealed T2 hyperintense, confluent, right-sided periventricular lesions (Fig. 2B), as well as lesions in the corpus callosum (Fig. 2C). Spinal cord MRI revealed multifocal, T2-hyperintense lesions in the cervical spine (Fig. 3A), which demonstrated faint enhancement on post-Gadolinium images (Fig. 3B).

Given the diagnostic impression that aPL-mediated antibodies were potentiating white-matter disease through both microangiopathic as well as inflammatory mechanisms (see Discussion below), the initial treatment regimen included prednisone 60 milligrams per

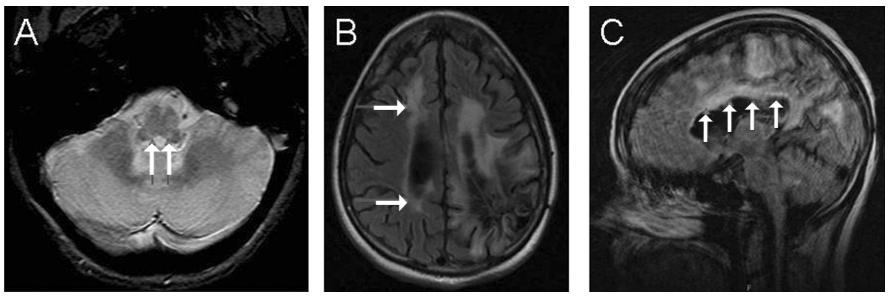

Fig. 2. MRI studies of the brain showing white-matter lesions remote from region of left AVM encephalomalacia. A) T2-weighted axial view of the brain shows hyperintense signals in the brainstem, including dorsal lesions (arrows) accounting for bilateral INO demonstrated in Figure 1. B) FLAIR-weighted axial view showing right-sided periventricular lesions (arrows), in addition to extensive encephalomalacia from left AVM resection. C) FLAIR-weighted sagittal view showing hyperintensities along the corpus callosun (arrows), in addition to corpus callosum atrophy.

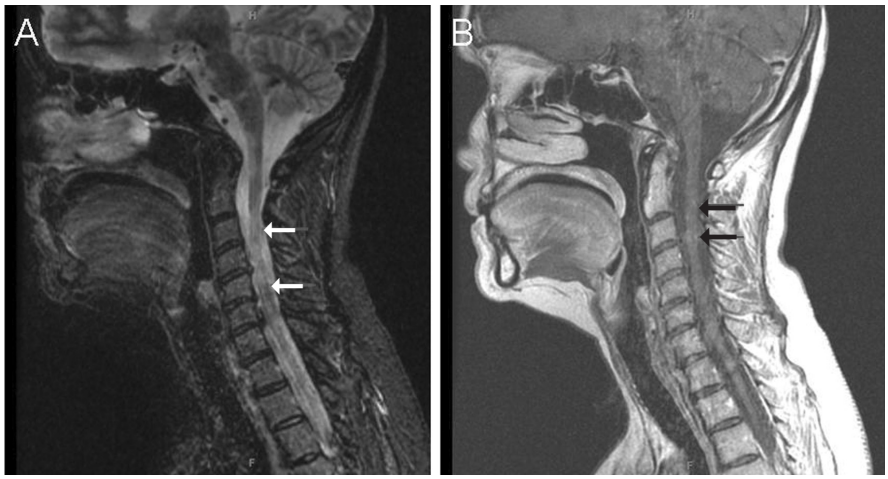

Fig. 3. MRI of spine. A) T2-weighted sequence demonstrating multifocal, hyperintense lesions (arrows) in the upper cervical spine. B) Post-Gadolinium, T1-weighted sequence showing faint, stippling enhancement (arrows) along the upper part of an atrophic cervical spine.

day, aspirin 325 milligrams per day, and mycophenolate titrated to 3000 milligrams per day. Although rituximab was considered, this was not reimbursed by the patient's insurance company. The prednisone was tapered and discontinued over four months.

After one month of this regimen, the patient was able to independently transfer, and was able to walk 50 feet with a cane. After one year of therapy, the patient can now walk nearly a quarter of a mile with a cane. She had normalisation of C3 levels, and improvement in C4 (6mg/dL-10mg/dL). Similarly, sequential neuroadiographic studies have shown no progression of white-matter disease, with serologies showing no change in the titers of her aPL antibodies. Her splinter haemorrhages have resolved, and the livedo reticularis rash is now less violaceous and intense.

Discussion

This report describes a patient who developed brainstem and spinal cord findings remote from left AVM encephalmalacia, curiously emerging after receiving experimental doses of radiation sufficient to induce symptoms of radiation toxicity. Such disseminated brainstem and spinal cord disease was felt to be reflective of MS. There is an extensive and often conflicting literature regarding the association of aPL antibodies to MS (5-12). However, MS can only be invoked as a culprit syndrome when there is no better diagnostic explanation (13). In general, CNS syndromes characterised by microangiopathic disease – including aPL syndrome – can cause clinical or MRI lesions which are similar to MS.

The patient had labs showing serial high-titer aPL antibodies, along with pleomorphic cutaneous features of aPL-mediated microangiopathic disease, including livedo reticularis, splinter haemorrhages, and abnormalities on nailfold capillaroscopy.

In patients with putative demyelinating syndromes, a chief diagnostic conundrum is distinguishing whether aPL antibodies are pathogenic, versus an epiphenomenon of a generalised inflammatory/autoimmune syndrome. In this patient, there were three iatrogenic triggers which likely colluded and enhanced the ability of aPL-antibodies to cause microangiopathic disease: (1) A history of radiation toxicity; (2). Treatment with beta-interferon; (3) Hypocomplementemia.

The pathogenicity of aPL antibodies can be modulated by additional, triggering causes of endothelial injury (14-15). Such additional triggers of endothelial injury have been demonstrated in experimental models as an important prerequisite of aPL-mediated microangiopathic injury (16-17). For example, Fischetti *et al* demonstrated that a "priming" dose of LPS administered intraperitoneally, was necessary to cause platelet and leukoaggregation in the smallest vessels of rats immunised with human aPL immunoglobulins (16). Similarly, the endothelial damage engendered by radiation toxicity may have served as an analogous trigger (18), and promoted a cascade of microangiopathic injury remote from the initial radiation site.

After receiving such "priming" doses leading to endothelial damage, regional prothrombotic or inflammatory triggers can further contribute to aPL-mediated endothelial perturbation. In this patient, the institution of beta-interferon was such an additional, iatrogenic trigger, which likely potentiated cutaneous as well as CNS disease. After treatment with beta-interferon therapy, the patient not only developed worsening neurologic disease (as evidenced by worsening spastic paraparesis), but then developed pleomorphic skin lesions of livedo reticularis, abnormal nailfold capillaries, and splinter haemorrhages. Rather than merely being temporally related to worsening CNS disease, the graduation from a CNS to a

systemic/cutaneous syndrome strongly implicates beta-interferon treatment as a direct culprit in aPL-mediated microangiopathic dysfunction.

This case constitutes the first example in the literature of beta-interferon causing both worsening skin and CNS manifestations of aPL-associated microangiopathy.

Although alpha-interferons are known to cause or potentiate autoantibody-mediated rheumatic diseases (including aPL antibodies and aPL syndrome) (19), only a single report has described the potential role of beta-interferon medications inducing aPL and other autoantibodies (20). In the context of a permissive cytokine spectrum, the institution of beta-interferon therapy – which leads to further elaboration of TH2 cytokines – may have unwittingly contributed to ongoing endothelial perturbation.

aPL-antibodies can modulate and promote a generalised state of endothelial perturbation. Pleiotropic mechanisms which have been suggested by *in-vitro* and animal models include upregulation of cell adhesion molecules (17) and tissue factor (21); biasing of eicosanoid metabolism towards thromboxane synthesis (22); inhibition of protein C and protein S (23); interference with the annexin V shield (24); endothelial apoptosis; and regional elaboration of IL-6 and a TH2 cytokine milieu (3).

Lastly, just as radiation toxicity and beta-interferon therapy constituted "second" and "third" hits exacerbating the CNS and cutaneous manifestations of aPL-mediated microangiopathy, the activation of the complement cascade likely served as a potent "fourth" hit. Recent studies have suggested that generation of C3a and C5a, as well as the C5b-9 Membrane Attack Complex, are potent anaphylotoxins which cause endothelial and platelet activation. In mice models, the C3 convertase inhibitor blocks aPL-mediated fetal loss (25), and mice deficient in C3 and C5 are resistant to fetal loss and aPL-induced endothelial activation (26). In humans, hypocomplementemia has been associated with thrombosis, livedo reticularis, and thrombocytopenia in primary APS (27-28). Regional activation of the complement cascade may overwhelm local inhibitory mechanisms which the endothelial cells use to regulate thrombophlebicity.

Rationale for treatment and patient's response

Although anticoagulation is warranted when aPL autoantibodies are associated with larger-vessel thrombotic episodes, it is unclear whether a similar strategy is warranted in aPL-mediated microangiopathic disease. Given that microangiopathic disease is characterised by endothelial as well as platelet interactions, we felt that antiplatelet treatment was indicated. Furthermore, this patient's transient improvement in symptoms after receiving intermittent doses of dexamethosone was intriguing. It was felt that immunosuppressive treatment would target the activation of complement, and other inflammatory mechanisms which were contributing to aPL-mediated microangiopathy. Indeed, Salmon *et al*. (29) have emphasised that the mechanism of complement-mediated inflammation is at least as important as thrombotic mechanisms in pregnancy loss. Especially given her symptomatic response to dexamethosone, it was felt that an empiric trial with immunosuppressant therapy was warranted.

Our patient's response to anti-platelet and immunosuppressive therapy similarly suggests that both prothrombotic as well as inflammatory mechanisms may be responsible for the evolution of CNS and cutaneous manifestations due to aPL-mediated microangiopathic dysfunction. Furthermore, the normalising complement levels further suggests an inflammatory mechanism which was interrupted by immunosuppresive therapy. Therefore, the recognition of aPL-mediated CNS microangiopathy as a distinct clinical entity might require different therapeutic strategies than currently used for strokes. Other mechanisms by which aPL-antibodies may promote CNS disease include distortion of endothelial tight-junctions (30), leading to disruption and "opening" of the blood-brain barrier. Furthermore, aPL antibodies may directly bind to neurons, and promote depolarisation (31).

White-matter lesions due to microvascular disease are believed to represent regions of chronic ischemia, not only due to "fixed" disease of end-territorial penetrating vessels, but also hypoperfused regions which can be salvaged with appropriate therapy (32). The patient's significant improvement in locomotor function suggests that white-matter dysfunction can be salvaged with appropriate treatment.

The limitation of this report concerns the inaccessibility of the CNS to histopathologic studies. It is acknowledged that this report lacks biopsy proof, about the progressive changes in the brain microvasculature. In this patient, the known association of CNS endothelial damage with radiation injury, and the amplification of brain and spinal cord disease clustered with worsening livedo reticularis rash, strongly argues for a microangiopathic basis for these lesions. Patients with vascular dementia may have a similar pattern of subcortical lesions which may be difficult to distinguish from MS. In these patients, histopathological studies have shown ischemic changes adjacent to hyalinised blood vessels (33). Although transependymal fluid can cause white-matter lesions on MRI (34), microangiopathic injury is significantly more likely when there are more confluent and numerous white-matter lesions, as is evidenced in this patient. Newer neuroimaging modalities, such as Magnetic Resonance Spectroscopy (MRS), may offer the possibility to investigate whether surrogate markers of ischemia – such as changes in the lactate peak – are associated with white-matter changes in aPL patients. This report emphasises such a need to incorporate such neuroimaging modalities. Additionally, it should be noted that microangiopathic injury in association with aPL antibodies more commonly occurs in "catastrophic" antiphospholipid syndrome.

In conclusion, a patient is presented who was misdiagnosed as MS, but with cutaneous and CNS manifestations due to aPL-mediated microangiopathic disease. In this patient, it is hypothesised that the history of radiation toxicity, the institution of beta-interferon therapy, and activation of the complement cascade contributed to endothelial perturbation. This case illustrates

that elucidation of other risk factors for small-vessel disease may be crucial in diagnosing and managing patients with microangioapthic syndromes associated with aPL antibodies.

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