Glomerular Fingerprint Deposits in A Young Woman with Stroke and Antiphospholipid Syndrome.

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Abstract

Ultrastructural evaluation of a renal biopsy specimen plays a pivotal role in accurately characterizing the types of renal involvement. We report a case of a 20 year-old woman, presenting with stroke with antiphospholipid syndrome, proteinuria (1.4 g per day), antinuclear autoantibody positive at 1:640 dilution, but negative anti-double-stranded deoxyribonucleic acid (anti-ds-DNA). Despite the negative anti-ds-DNA, we still strongly suspected systemic lupus erythematosus (SLE) with renal involvement. Angiography was suggestive of vasculitis, so methylprednisolone pulse therapy was started, followed by oral prednisolone. On renal biopsy, fingerprint deposits were diagnosed on electron microscopy, and the pathologic diagnosis was Class III lupus nephritis. Fingerprint deposits are found in SLE and mixed cryoglobulinemia. But our case had negative cryoglobulin. A repeat test for anti-ds-DNA using a different method was positive. The patient completely recovered neurologically about six months after presentation. This case illustrates the importance of actively pursuing the diagnosis of SLE when there is a high index of suspicion for this disease. (J Intern Med Taiwan 2002;13:31-37)

Key Words：Fingerprint deposits, Anti-ds-DNA, Antiphospholipid syndrome.

Introduction

Fingerprint deposits in glomeruli consist of alternating dark and light bands, sometimes straight, but often curved as if arranged around a center. They represent an organized or crystalline pattern of immune complex, and it has been proposed that they develop from crystallized DNA [1]. They are found in SLE and mixed cryoglobulinemia.

Antiphospholipid syndrome (APS) is a term used to describe the combination of clinical features, including both venous and arterial occlusive events, recurrent spontaneous abortions, and thrombocytopenia, with antiphospholipid antibodies (APAs) [2].

There is an increasing evidence of an association between elevated APAs level and stroke in young and middle-aged adult [3]. APAs with neurological lesion may occur in SLE [4] or non-SLE patient [3,5,6].

We report a case of a patient with these findings and discuss her diagnosis.

Case Report

A 20-year-old Chinese woman was admitted complaining of left-sided weakness for 2 days. She had suffered from common-cold-like symptoms two weeks previously and visited a Chinese medicine practitioner, who prescribed Chinese herbs. She also noticed a severe throbbing headache, predominantly in the right temporal area, but not associated with nausea, vomiting, or fever. The headache subsided a few days later. One day prior to admission, she felt weakness in her left hand while lying in bed but initially didn't think it indicated anything unusual. However, it became increasingly severe and was followed by numbness and pain on the left side of her body. She denied joint pain, oral ulcers, photosensitivity, skin rash, impaired vision or Raynaud's phenomenon. She denied any history of systemic disease. There was no family history of autoimmune disease, cerebrovascular disease, or cardiovascular disease. She denied taking oral contraceptive pills or other medication except for the Chinese herbs noted above.

On physical examination, she was drowsy and appeared acutely ill. She was afebrile and normotensive. Pupils were 2.0 mm bilaterally, with a positive light reflex. She had no neck stiffness, lymphadenopathy, facial palsy, or malar rash. The pulmonary and cardiovascular examinations were normal, with no heart murmur detected. The abdominal examination revealed no splenomegaly. Neurological examination disclosed muscle power of 2-3/5 in the upper and lower left extremities, a Barbinski sign on the left, and impaired sensation over the left half of the body. No pitting edema in extremities.

A lumber puncture yielded clear, watery CSF; Pandy's test was negative, there were no cells, and the glucose was 49 mg/dl (45-75), protein 35 mg/dl (10-45), Cl 126 mEq/L (118-132), and LDH 17 (8-12). Her WBC count was 7700, with 0 bands, 71 neutrophils, 0 basophils, 0 eosinophils, 9 monocytes, and 20 lymphocytes; the hemoglobin was 9.9 g/dl, hematocrit 33.6%, platelets 443,000 /μl, PT: 11.5 sec (control 11), aPTT: 27 sec (control 30), bleeding time 2 min, and ESR 55 mm (10-20 mm/ first hour by Westergren). Urinalysis disclosed 1+ protein, RBC 1/HPF, WBC 2/HPF, epithelial cells 1/HPF, and no cellular casts. BUN was 11 mg/dl, creatinine 0.7 mg/dl, and urinary protein 1.4 g/24 hours. Serum electrolytes and liver function were normal. Total protein was 6.5 g/dl, albumin 2.8 g/dl, triglycerides 126 mg/dl, cholesterol 205 mg/dl, glucose （AC） 93 mg/dl. Her anemia was further investigated: the MCV was 70.6 μm^3 (83-95μm^3), MCH 20.8 pg/cell (27-32 pg/cell), MCHC 29.4 g/dl (32-35 g/dl), iron 55μg/dl (37-170 mg/dl), TIBC 250μg/dl (260-445 mg/dl), ferritin 30 ng/ml (10-150 ng/ml). Her C3 was 101 mg/dl (90-150 mg/dl), C4 13 mg/dl (17-37 mg/dl), RA factor <20 IU/ml (< 20), and ANA positive at 1:640 dilution with a speckled pattern, anti-ds-DNA by radioimmunoassay (RIA) (Farr assay, DPC anti-DNA, Diagnostic Products, Los Angeles, CA) was 4.62 IU/ml (<5.3 IU/ml). A rapid plasma reagin test was non-reactive. Protein S was 185% (55-160%), protein C 109% (70-140%), and antithrombin Ⅲ 83% (80-130%). Anti-cardiolipin (ACL) IgG was 25.5 GPL U/ml (<10), anti-cardiolipin IgM 2.5 MPL U/ml (<7), and LE cell by latex preparation was negative. ENA screening was positive, anti-Sm negative, anti-RNP negative, anti-SSA positive, anti-SSB negative, cANCA (antineutrophil cytoplasmic antibobodies) negative, pANCA positive, and cryoglobulins negative.

Brain CT (Fig 1a) was suggestive of a focal ischemic infarct involving the posterior limb of the right internal capsule and a portion of the right thalamus. EEG showed a focal destructive lesion in the right hemisphere. Magnetic resonance imaging (Fig 1b) revealed a focal ischemic infarct involving the posterior limb of the right internal capsule, right thalamus, right cerebral peduncle. Angiography (Fig 2) disclosed focal segmental irregular narrowing just distal to the plexal point of the right anterior choroidal artery, findings suggestive of vasculitis. Carotid duplex sonography showed a high resistance flow profile in the right and left common carotid arteries, suggesting increased downstream vascular resistance such as with distal stenosis, poor cardiac performance. Real time imaging revealed no evidence of plaque formation. A Doppler study showed an irre-gular signal and rounding of the systolic peak in the subclavian arteries bilaterally, consistent with stenosis. There was diminished flow in the right vertebral artery with a small caliber vessel but normal ophthalmic flow. Heart echo showed normal left ventricular systolic and diastolic function and no ob-
vious intracardiac thrombus. Transesophageal
echocardiogram revealed no thrombus in the left atrium or ventricle and no vegetations. There was hypertrophy of the left papillary muscle and thickening with early sclerosis of the non-coronary aortic cusp, with prolapse. Renal echo showed normal-sized kidneys with normal parenchymal echogencity.

The patient was diagnosed initially with left cerebral infarct due to cerebral thrombosis with APS and was treated with heparin. Her clinical features of cerebral thrombosis, proteinuria, positive ANA, IgG ACL and anti-SSA, were highly suggestive of SLE, although the negative anti-ds-DNA was confusing. However, lupus renal disease was significantly possible. Angiographic finding was suggestive of vasculitis. Therefore methylprednisolone pulse therapy was started, followed by oral prednisolone 60 mg/day.

A renal biopsy was done (Fig 3). Light microscopy (LM) of the specimen showed segmental endocapillary proliferation in some glomeruli. There was no leukocyte infiltration or crescent formation, nor were subendothelial hyaline deposits identified. Apoptotic bodies were present, and both tubules and interstitium were unremarkable. Immunofluorescence microscopy (IFM) revealed IgG (+1), IgM (+1), IgA (-), C3 (+2), C1q (+2), kappa (+1), lambda (+1). On electron microscopy (EM), there were electron dense deposits in the mesangium and occasionally in the subepithelial regions. The foot processes of the podocytes were effaced. The organized electron dense deposits were composed of fingerprints and parallel arrays of paired, linear electron dense filaments with a central lucency. The final pathological diagnosis was lupus nephritis, class III, with an activity index of 4 out of 6 and a chronicity index of 1 out of 4.

Given the biopsy diagnosis, we seriously questioned the results of the Farr assay for anti-ds-DNA and decided to reevaluate the initial blood sample using an indirect fluorescent antibody test (IFA) with a nDNA Fluoro-Kit^{TM} (Crithidia luciliae assay). The result was positive at a 1:320 dilution.

The patient had fully recovered neurologically by about six months after presentation. She remains on maintenance therapy with oral prednisolone.

Discussion

Our patient's initial presentation (Table1)

Table 1. Revised criteria for diagnosis of SLE 7 and positive findings in our patient

Criteria for diagnosis of SLE	Sensitivity%	Specificity%	Our patient
1.Renal involvement (proteinuria >0.5g/d,cellular cast)	51	94	+
2.CNS involvement	20	98	+
3.ANA	99	49	+
4.Immunological disease (anti-ds DNA, Anti-sm Ab, false positive test for syphilis, positive LE preparation)	85	93	-
5.Hematological disorder	59	89	-
6.Malar rash	57	96	-
7.Discoid rash	18	99	-
8.Photosensitivity	43	96	-
9.Oral ulcer	27	96	-
10.Arthritis (two or more joints)	86	37	-
11.Serositis	56	6	-

was very suggestive of SLE, in that she was female, had a stroke at a relatively young age, had proteinuria of 1.4 g/day, and an ANA positive at a 1:640 dilution. However, she did not initially fulfill the criteria for SLE published by the American College of Rheumatology (ACR) [7]. According to those guidelines, four criteria are acceptable for the diagnosis of SLE with 98% specificity and 97% sensitivity. Rather than having definite hemolytic anemia, hers was microcytic in nature. Also, the initial anti-ds DNA titer was below the level of significance on the Farr assay. The ANA is reported to be 99% sensitive but only 49% specific for the diagnosis of SLE [7]. It can be found in healthy persons, the elderly, in other rheumatic or non-rheumatic diseases, and in family member of patients with SLE [8]. Anti-ds-DNA and anti-SSA are associated with lupus nephritis, and the latter was positive in our patient. Renal involvement is more common in younger patients, especially younger than 30 years, and it often develops early in the disease process [9]. The patient's APS, with an increased titer of IgG ACL, was not specific for SLE, as it can occur and cause cerebrovascular disease even in the absence of any other findings suggestive of lupus. However, given the range of the patient's abnormalities, we still strongly suspected SLE with renal involvement.

Renal biopsy is indicated when there are non-conclusive clinical or serological markers that the patient has SLE, and/or to determine the type, degree of activity and chronicity of renal involvement, and the appropriate treatment plan [10]. Early aggressive treatment is required for proliferative lupus nephritis to avoid irreversible parenchymal damage [11].

In our patient, the findings on LM were not totally consistent with the typical findings in SLE. The latter include segmental or global, focal or diffuse hypercellularity of the glomerular tuft due to proliferation of mesangial, endothelial, and epithelial cells, and

some degree of monocyte or polymorphonuclear cell infiltration. Fibrinoid necrosis, hematoxylin bodies, hyaline thrombi, and wire loop are also commonly seen.

A full house of immunoreactants (ie, IgG, IgM, IgA, C_3, C_4 or C_{1q} , kappa and lambda) is found in 25% of patients with lupus nephritis and is highly characteristic of it [12,13].

A fingerprint deposit can be seen in 6-10% of cases of lupus nephritis on EM. This finding is regarded as a sensible marker for concomitant renal disease or subsequent development of overt lupus nephritis [14]. It can also be found in the mixed cryoglobulinemia [15-17]. Our patient, however, did not have cryoglobulinemia. The presence of fingerprint deposits plus a full-house immunofluorescence profile make the diagnosis of SLE highly likely[15]. Fingerprint deposits were used to diagnose silent lupus nephritis in the presence of a normal urinalysis by Tojo, et al [18]. The fingerprints morphologically represent a homogenous group of organized deposits unrelated to cryoglobulins and diagnostically relevant for SLE [19].

EM plays a pivotal role in accurately characte-rizing the type of renal involvement . It is the most useful in examination of glomerular lesions, definitive localization of immune complex deposits within glomerulus and the characteristic substructure of immune complexes in cryoglobulinemic glomerulonephritis including SLE [20], amyloidosis [21], kappa light chain disease [22], fibrillary glomerulonephritis [23], and immunotactoid glomerulopathy [24]. EM provides clinically meaningful information in 45% of cases of lupus nephritis [25]. It also indicates the degree of disease activity and provides a useful guide for management [26-28].

Given our patient's biopsy results, along with the other manifestations of her disease, we felt confident in finally making a definitive diagnosis of SLE. The only remaining puzzle was the non-diagnostic anti-ds-DNA titer.

The anti-ds DNA antibody is 85% sensitive and 93% specific for the diagnosis of SLE [7]. The Farr assay is a radioassay based on ^{125}I-labeled recombinant DNA and is designed for the quantitative measurement of anti-ds-DNA antibody in serum. As noted above, we retested our patient's initial blood spe-cimen with a nDNA Fluoro-Kit ^{TM}, the result was definitely positive. This test is used for detection and titration of circulating native DNA autoantibodies in human serum using the hemoflagellate Crithidia luciliae. The Farr assay has been reported to be the most sensitive assay for anti-ds DNA Ab [29], but at least in our case, this was not borne out. It may be that different types of antibody bind to different sites depending on the manufacturer, or it may simply have been a false negative.

Harris et al defined APS as a combination of clinical features, including both arterial and venous occlusive events, recurrent spontaneous abortion, thrombocytopenia, and APAs, which consist of moderate to high titers of IgG or IgM ACL or lupus anticoagulant LA[2]. The APAs are heterogeneous groups of circu-lating immunoglobulins directed against anionic phospholipids present in the cell membrane [3]. These antibodies are found in 1-2% of healthy individuals [30], in 33-40% of patients with SLE, and in 50% of patients with SLE who have neurological lesions [4]. Four types of neurological disorder may be seen in patients with APAs: cerebral infarction, ischemic visual abnormalities, migraine-like headache, and encephalopathy. There is an increased prevalence of APA in many non-SLE patients with ischemic

cerebrovascular disease or other unexplained thrombosis [3,5,6]. The majority of thrombotic events in patients with APAs are venous, frequently recurrent, and often result in pulmonary embolism. If thrombosis occurs in the arterial circulation, the brain is most affected [6,31].

This case demonstrates the importance of maintaining a high index of suspicion for SLE, particularly in a young woman with stroke and APS, even though clinical and labortory criteria may not fulfill the typical diagnostic criteria. Although the ACR criteria are very helpful in standardizing diagnostic criteria so that patient groups in various investigations can be compared, they should not necessarily be used to exclude the diagnosis in an individual patient. If SLE is strongly suspected, it is important to pursue the diagnosis vigorously, including the use of invasive procedures and ultrastructural evaluation if deemed necessary.

Conclusion

Ultrastructural evaluation of a renal biopsy spe-cimen may be crucial in the diagnosis of SLE, especially in a patient who, at the time of biopsy, lacks either adequate clinical manifestations and /or serologic markers to make the diagnosis [32]. If the initial result of anti-ds DNA is negative, the test should be repeated using another method. The diagnosis must not be excluded prematurely without searching very hard for confirmatory evidence.

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Fig.1a. Brain CT demonstrated focal ischemic infarct involving the posterior limb of the right internal capsule and a portion of the right thalamus.
Fig.1b. Magnetic resonance imaging revealed a focal ischemic infarct involving the poste-
rior limb of the right internal capsule, right thalamus, right cerebral peduncle.

Fig.2. Angiography disclosed focal segmental irre-gular narrowing just distal to the plexal point of the right anterior choroidal artery, findings suggestive of vasculitis.

Fig.3. Electron Microscopy disclosed the organized electron dense deposits exhibit various features. Among them, the most striking is the fingerprint substructure. It consists of para-
llel arrays that displays dark bands alterna-
ting with light bands.

發現腎絲球指紋狀沉澱物於抗磷脂症候群及腦中風之年輕女性病患

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摘　　要

要確立診斷不同型態之腎臟病，腎組織切片之超微結構評估佔有樞紐性地位。我們報告一位 20 歲女性病人，有抗磷脂症候群，蛋白尿一天 1.4 克，抗細胞核自體抗體（ANA）1：640，發生了腦中風。但沒有抗雙螺旋鏈去氧核醣核酸（anti-ds-DNA）。雖然沒有抗雙螺旋鏈去氧核醣核酸，我們仍然強烈懷疑紅斑性狼瘡合併腎病變。血管攝影顯示血管炎。因此給予脈衝甲基去氫氧化可體松(methylprednisolone)靜注後給予口服類固醇。腎臟切片時，在電子顯微鏡下發現指紋狀沉澱物，病理診斷爲 classⅢ狼瘡性腎炎。紅斑性狼瘡及冷凝球蛋白血症之組織切片均可有指紋狀沉澱物，而我們的病人並沒有冷凝球蛋白。因此使用不同方法重測 anti-ds-DNA 時卻呈正反應。六個月後病人之神經症狀完全恢復。本病例說明了當高度懷疑紅斑性狼瘡時積極追查之重要性。