



Concurrent Presentation of Thrombotic Thrombocytopenic Purpura and Membranous Nephropathy

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INTRODUCTION

Acquired thrombotic thrombocytopenic purpura (TTP) is a hematologic emergency associated with decreased thrombospondin motifs 13 (ADAMTS13, a disintegrin and metalloproteinase with thrombospondin motifs 13) activity, due to the presence of an inhibitor. Idiopathic membranous nephropathy related to the anti-phospholipase A2 receptor (anti-PLA2R) can coexist with other autoimmune diseases. Herein, we present a case of a 70-year-old man who presented with generalized anasarca and thrombocytopenia.

CASE PRESENTATION

A 70-year-old African American male patient was transferred to our hospital with a 3-day history of dyspnea and chest discomfort. He described non-radiant substernal chest pressure and progressive shortness of breath with exertion that improved with rest. He also reported new-onset edema in his legs and hands over the last 3 weeks. He denied hematuria or dysuria, but reported foamy urine. He also denied fever, chills, headache, vision problems, nausea, vomiting, abdominal pain, diarrhea, skin rash, or joint pain. His medical history was remarkable for untreated hepatitis C, type 2 diabetes mellitus, bladder cancer status postresection >5 years previously, Barrett’s esophagus, and schizophrenia. He had no symptoms of retinopathy or neuropathy. He reported a long smoking history and a remote history of drug abuse, mostly methamphetamine and cocaine. His medications included finasteride, metformin, olanzapine, omeprazole, and simvastatin. He

was afebrile; other vital signs included pulse in the 80s, blood pressure 180/100 mm Hg, and oxygen saturation of 97% (room air). Physical examination was remarkable for elevated jugular vein pressure, bilateral rales, and 2+ lower extremity edema. Initial laboratory workup is shown in [Table 1](#). He was admitted for management of non–ST-segment elevation myocardial infarction. Heparin was not given because of thrombocytopenia. Hematologic findings were consistent with thrombotic thrombocytopenic purpura (TTP). von Willebrand factor protease (a disintegrin and metalloproteinase with thrombospondin motifs 13 [ADAMTS13]) activity level was assessed. An apheresis catheter was placed, and the patient was started on plasma exchange and prednisone 1 mg/kg. Renal ultrasound showed normal-sized kidneys. Ophthalmologic evaluation found minimal signs of diabetic retinopathy.

The renal team decided to proceed with renal biopsy because nephrotic-range proteinuria is unusual for TTP. Biopsy showed features of membranous nephropathy (MN). The deposits were immunoreactive for phospholipase A2 receptor (PLA2R) and IgG, which was restricted to the IgG1 subclass ([Figure 1a](#) and [b](#)). Many of the subepithelial deposits were flanked by new basement membrane material (“spikes”), which suggested some element of chronicity to this process ([Figure 1c](#)); and which were classified as stage II deposits according to the criteria by Ehrenreich and Churg.¹ In addition, the patient had moderately severe arterial and arteriolar sclerosis and segmentally prominent double contour formation in the glomeruli that were not spatially associated with immune complex

Table 1. Laboratory and radiographic investigation on initial presentation

HGB	7.4 mg/dl (was normal 5 months previously)
WBC	9.2 K/ μ l (ref range: 4–11)
Platelets	36 K/ μ l (was normal 5 months previously)
Sodium	143 mEq/l
Potassium	4.5 mEq/l
Chloride	112 mEq/l
Bicarbonate	25 mEq/l
Creatinine	1.43 mg/dl (1 mg/dl 5 months ago)
Troponin I	6.4 ng/ml (ref range < 0.03 ng/ml)
BNP	551 pg/ml
CXR	Bilateral pleural effusions
ECG	Nonspecific T-wave changes
Coagulation labs	INR 1.01, PTT 48,
Hemolysis labs	LDH 742 U/l (ref range: 171–308), haptoglobin undetectable, direct Coomb's test negative
Peripheral blood smear	Many schistocytes
Urine analysis (UA)	UA shows 2+ blood, 3+ protein.
Urine microscopy	Few dark brown pigmented casts, oval fat bodies, many transitional cells, some RBCs, no RBC casts or WBC casts
Complement	Normal
Infection serology	HIV negative. HCV positive (known)
ANCA	Negative
Lupus, antiphospholipid, serology	ANA, negative. Lupus anticoagulant, Cardiolipin Ab, and β 2-glycoprotein were absent.
Electrophoresis	Serum and urine protein electrophoresis were normal
Cryoglobulins	Negative
Urine protein/creatinine (Cr) ratio	9 g/g Cr
Serum albumin	2 mg/dl

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; BNP, brain natriuretic peptide; CXR, chest X-ray; ECG, electrocardiogram; HCV, hepatitis C virus; HGB, hemoglobin; INR, international normalized ratio; LDH, lactate dehydrogenase; PTT, partial thromboplastin time; RBC, red blood cell; WBC, white blood cell.

deposition. These vascular changes suggested a primary form of endothelial injury, consistent with chronic thrombotic microangiopathy.

The platelet count of the patient normalized after 3 days of daily plasma exchanges; this rapidity of response was not expected. von Willebrand factor protease activity was <3% (reference range: 68–163%), and an ADAMTS13 inhibitor was present at a titer of 1.3 (reference range: <0.4 Bethesda equivalent units). Multimeric analysis of von Willebrand factor antigen was normal. Anti-PLA2R was detected in the serum at a titer of 40.3 RU/ml.

METHODS

Recombinant human ADAMTS13 was obtained as cell lysate from Dr. Evan Sadler, Washington University, St. Louis, Missouri. Equal amounts were electrophoresed under nonreducing conditions, transferred to nitrocellulose, and Western blotted using serum from the patient, control serum, or a commercial antibody

against the StrepTag on the recombinant protein. Human IgG1 was detected with an IgG1 subclass specific sheep antibody (The Binding Site, Birmingham, UK). Serum from the patient was collected immediately after plasma exchange treatment, and at 1 and 2 months of follow-up. These sera, as well as serum from a normal control, were used to assess reactivity to recombinant human ADAMTS13, as well as the 2 known autoantigens in primary MN (PLA2R and thrombospondin type-1, domain-containing 7A [THSD7A]).

Human glomerular extract (HGE), recombinant PLA2R, and recombinant human THSD7A were prepared as described^{2,3} and gel electrophoresed as previously described. In addition, a StrepTag- (IBA Lifesciences, Göttingen, Germany) and hexahistidine-tagged human PLA2R cysteine-rich (CysR) domain construct was expressed in HEK293 cells, and the secreted product was run by sodium dodecyl sulfate polyacrylamide gel electrophoresis under nonreducing conditions. After transfer to nitrocellulose, these products were Western blotted with patient or control serum, and assayed for the IgG1 or the IgG4 subclass of IgG.

RESULTS

Immunoblot of rhADAMTS13 with a commercial antibody that recognized the StrepTag revealed the full-length product (1398 amino acids) and 3 smaller degradation products (Figure 2a). Notably, these 4 ADAMTS13 bands, when detected for IgG1, were found in the serum from the patient, both after plasma exchange and at 1-month follow-up. A control serum exhibited no reactivity.

We next tested the serial serum samples from the patient by Western blot against a detergent extract of human glomerular proteins (HGE), as well as cell-expressed recombinant human PLA2R and THSD7A. The initial sample was reactive with native (in HGE) and recombinant (cell-expressed) PLA2R, mostly of the IgG1 subclass with a minor amount of IgG4 (Figure 2b). There was no reactivity with human THSD7A. The follow-up sample showed nearly equivalent amounts of IgG1 anti-PLA2R, although the IgG4 band had disappeared.

Figure 2c demonstrates the continued presence of anti-PLA2R in the initial, and 1- and 2-month-follow up samples. We tested for reactivity to the CysR and the first C-type lectin-like (CTLD1) domains of PLA2R to assess whether any epitope spreading had occurred. The patient serum was only reactive with the immunodominant CysR domain.

DISCUSSION

Acquired TTP is characterized by diminished ADAMTS13 activity due to acquired autoantibody

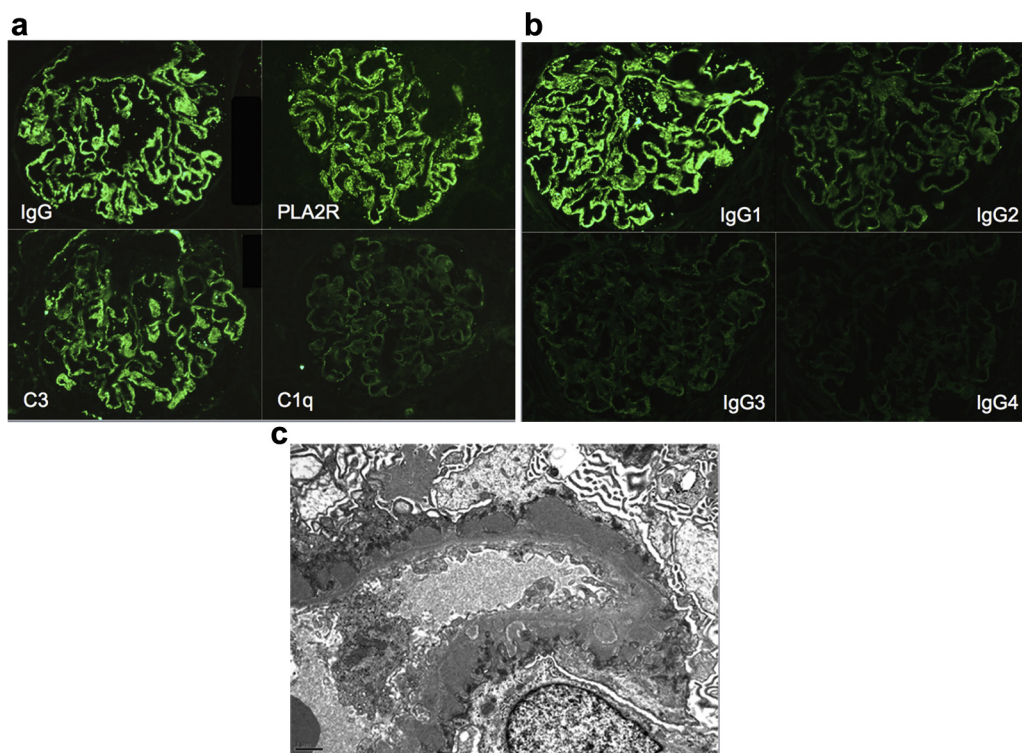


Figure 1. Histopathologic images of the kidney biopsy. (a) Immunofluorescence microscopy images of frozen kidney biopsy sections showing positive staining for IgG, phospholipase A2 receptor (PLA2R), and C3 in a peripheral capillary loop fine granular pattern. C1q is negative. (b) Immunofluorescence detection of human IgG subclasses demonstrates that IgG1 is predominant, with virtually no IgG4 staining. (c) Electron micrograph showing the stage II subepithelial electron-dense deposits, as well as some swelling and loss of fenestrations of the capillary endothelium.

inhibitors. Plasma ADAMTS13 normally cleaves von Willebrand factor after secretion and within thrombi. ADAMTS13 deficiency perturbs the regulation of the size of von Willebrand factor multimers, which leads to diffuse microthrombi, microangiopathic hemolysis, thrombocytopenia, and tissue ischemia.⁴

More than 90% of patients with acquired TTP and severe ADAMTS13 deficiency have circulating anti-ADAMTS13 in the plasma.⁵ Most of these antibodies are inhibitory. Circulating antibodies are targeted against the primary epitope in the ADAMTS13 spacer domain (see Figure 3) in up to 97% to 100% of cases, with the amino acids Arg568, Phe592, Arg660, Tyr661, and Tyr665 as the primary antigenic targets.⁵ Moreover, antibodies that recognize epitopes in other ADAMTS13 domains are found in up to 64% of cases.^{5–8} Antibodies are predominantly of the IgG4 subclass (90%), followed by IgG1 (53%), IgG2 (50%), and IgG3 (33%).^{5,9} Titers of IgG4 and IgG1 subclasses are inversely correlated.¹⁰ A subclass profile characterized by high levels of IgG4 seems to be predictive of a more responsive form of TTP compared with those with IgG1.¹⁰ However, high titers of IgG4 have been associated with an increased risk of relapse,⁹ whereas the presence of IgA or IgG1 has been associated with poor and sometimes lethal outcome at the first episode.^{9,11}

MN was attributed to formation of antibodies against podocyte antigens. Beck *et al.*³ identified PLA2R as the major antigen in MN, associated with 70% of cases. PLA2R is a member of the mannose receptor family, which shares a common domain structure.¹² Several studies using x-ray crystallography were performed on mannose receptor members to predict the structure and function of individual domains, particularly the N-terminal CysR domain.¹³ It was suggested that the 3-dimensional conformational structure is an essential feature of PLA2R epitope, and that pH-dependent conformational changes could lead to certain epitope exposure.³ The dominant epitope that interacts with human anti-PLA2R autoantibodies is located in the N-terminal CysR (ricin B) domain.¹³

Although the pathogenicity of anti-PLA2R autoantibodies has not been conclusively confirmed, several observations support this hypothesis: the presence of PLA2R within immune deposits; the correlation of anti-PLA2R antibody titers and disease activity; and the elution of anti-PLA2R antibodies from glomerular extracts.¹⁴ In contrast, the absence of anti-PLA2R in secondary MN and other glomerular diseases argues against anti-PLA2R being a biomarker of the disease process or generally reflective of podocyte damage.¹⁴ In primary cases, IgG4 is the predominant IgG subclass

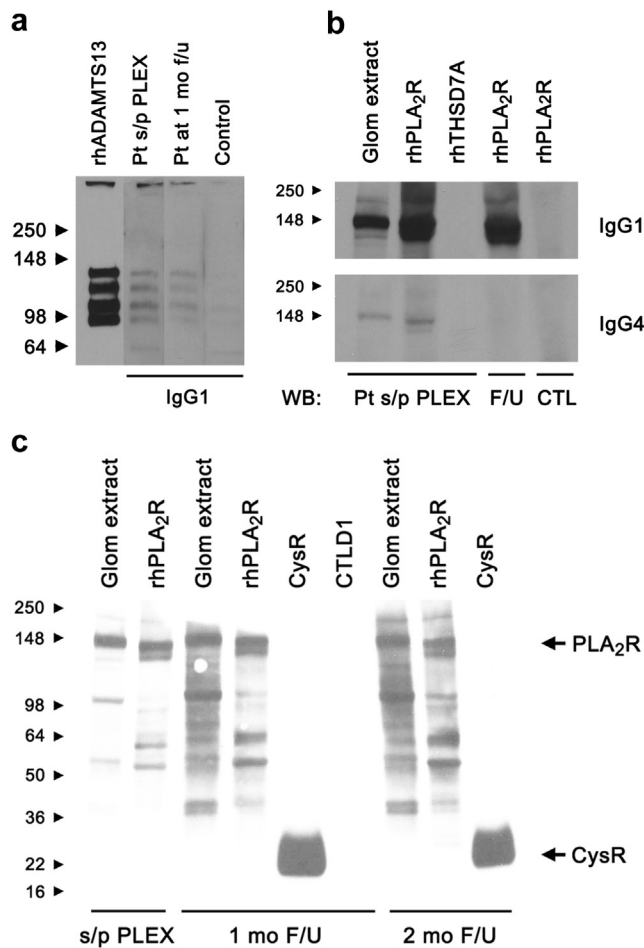


Figure 2. Western blots (WB) using serial serum samples from the patient (Pt) just after plasma exchange (PLEX), and at the 1- and 2-month follow up. (a) Recombinant human (rh) a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13) tagged with a StrepTag was electrophoresed in all lanes. Anti-StrepTag (left lane) recognizes the full-length protein and the 3 degradation products. Serum from the patient and detected for IgG1 exhibits the identical bands, whereas control (CTL) serum gives only minimal background staining. (b) Human glomerular extract, recombinant human phospholipase A2 receptor (rhPLA₂R), and recombinant human thrombospondin type-1 domain-containing 7A (rhTHSD7A) were immunoblotted with the patient (vs. control) serum after PLEX or at 1-month follow up (F/U), and detected for IgG1 and IgG4. The predominant reactivity is the IgG1 subclass against PLA₂R, with no reactivity detected against THSD7A. (c) Glomerular extract, recombinant PLA₂R, and the individual cysteine-rich (CysR; lower arrow) or first C-type lectin-like domain (CTLD1) from human PLA₂R were immunoblotted with patient serum from the 3 time points and detected for IgG1. Only the CysR domain of PLA₂R was recognized, and not the CTLD1 domain. The position of PLA₂R is shown by the upper arrow, and the lower bands are nonspecific reactivity to other glomerular or cell-expressed proteins, typically seen when detecting for IgG1.

within subepithelial deposits, which has been found in >75% of cases, whereas other subclasses predominate in secondary forms of the disease, such as those associated with autoimmune diseases or malignancy, in which IgG1 is predominant in approximately 60% of

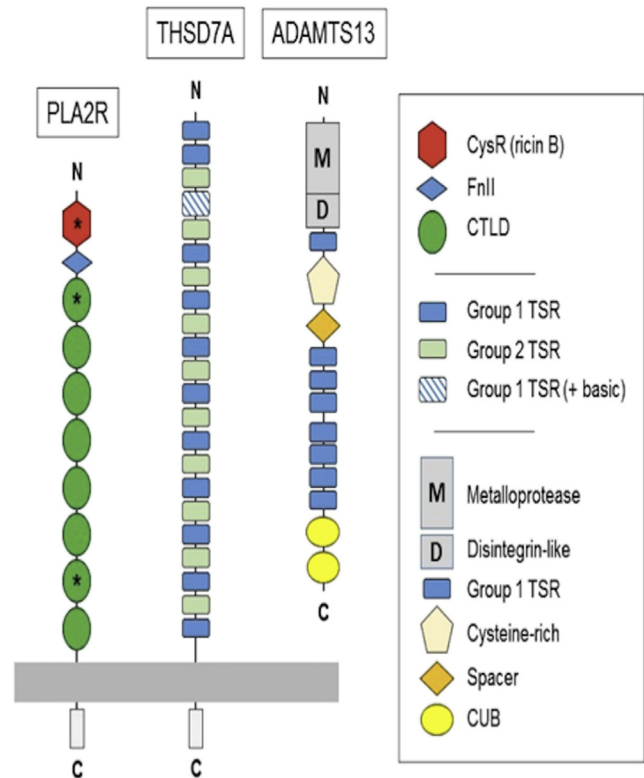


Figure 3. Schematic of the domain structures of phospholipase A2 receptor (PLA₂R), thrombospondin type-1 domain-containing 7A (THSD7A), and a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13). The PLA₂R and THSD7A are both large transmembrane glycoproteins with short cytoplasmic tails. ADAMTS13 is a secreted protein that contains group 1 thrombospondin type-1 repeats, similar to THSD7A. It also contains a cysteine-rich domain (CysR), but it is distinct from the CysR of PLA₂R. The individual domains are denoted in the box. Asterisks indicate domains in PLA₂R that contain known humoral epitopes. The fourth TSR of THSD7A is degenerate and contains a large region rich in basic amino acid residues. CTLD, C-type lectin-like domain; CUB, complement C1r/C1s, Uegf, Bmp1 domain; FnII, fibronectin type-2 domain; TSR, thrombospondin type-1 repeat.

cases.¹⁵ Consistent with the inability of IgG4 to activate the complement pathway, C1q staining is often absent or weak in biopsy specimens of primary MN. Conversely, it is prominent in other autoimmune diseases (e.g., lupus). C4 has been demonstrated in immune deposits of primary MN, potentially implicating the lectin pathway.^{16,17} There is some evidence that IgG4 anti-PLA₂R autoantibodies can bind mannan-binding lectin and activate this pathway.¹⁸ Anti-PLA₂R is increasingly being used to monitor disease activity and predict response to treatment and relapse risk.¹⁹

Nephrotic range proteinuria in the setting of TTP was reported in patients with systemic lupus erythematosus (SLE). In a large series of patients with TTP, 23% of patients had some pathological findings that suggested SLE. In most cases, Libman-Sachs endocarditis was the only finding to indicate SLE. Only 4%

had evidence of glomerular pathology.²⁰ Our case serology was completely negative for lupus, with no evidence of lupus nephritis on biopsy. IgG1 surprisingly consisted of most of the anti-PLA2R autoantibodies (accompanied by only minor amounts of IgG4) in both the subepithelial deposits on biopsy and by Western blot for PLA2R. This contrasted with reports that IgG4 was the predominant subclass for both TTP and MN. The presence of IgG1 against PLA2R in our case might have been crucial for disease development. There was the possibility that testing was confounded by the specimen being obtained after the initiation of the first plasma exchange. However, plasma exchange is not known to remove IgG subclasses differentially.²¹

An attractive hypothesis to explain the coexistence of these 2 disease entities is that a single pathogenic antibody might target a similar conformational epitope carried by both antigens. We interrogated whether any of the different epitopes known to be involved in the humoral response in MN exhibited any homology with domains within ADAMTS13. The presence of any potential homology could lead to epitope spreading, which was implicated in the pathogenesis of these 2 entities.^{22,23} ADAMTS13, similar to PLA2R, contains a region called a Cys-rich domain, which is located at the C-terminal to the first thrombospondin repeat and before the spacer region. When we compared that region of ADAMTS13 against all human proteins using Protein BLAST (National Center for Biotechnology Information, U.S. National Library of Medicine, Bethesda, MD), the only homologies found were with other ADAMTS proteins, and not PLA2R. We directly compared the ADAMTS13 CysR domain with the PLA2R CysR domain, and there was no homology. Therefore, it was unlikely that there was a common epitope in the respective CysR domains of the 2 autoantigens, despite the serum from this patient recognizing the CysR domain of PLA2R.

The newly described antigen in MN, THSD7A,² is composed of repeating thrombospondin type-1 repeats that are similar to those in ADAMTS13. This raised the question whether our patient, in addition to possessing autoantibodies to PLA2R, might also carry anti-THSD7A antibodies, and that this shared epitope could explain the presence of the 2 autoimmune diseases. However, we did not find anti-THSD7A in this case.

Despite the absence of autoantibodies targeting an epitope shared between the 2 molecules, these 2 autoimmune processes were also related because both autoantibodies were predominantly of the IgG1 subclass, instead of the more common IgG4 subclass. IgG1 might be dominant in the early phases of MN, because it is

found in 64% of cases, and might possibly play a crucial role in early disease pathogenesis by activating the classical complement pathway.¹⁵ The predominance of IgG1 against both ADAMTS13 and PLA2R might also have been directed by Th1 cytokines driven by an underlying inflammatory state or could instead represent an early, and perhaps, aggressive form of these 2 diseases.

MN has been described in other autoimmune diseases like Grave's disease, celiac disease, and others. One assumption is that patients with these diseases have a perturbed immune system and/or carry particular human leukocyte antigen haplotypes associated with autoimmune disease, which makes them more susceptible to also developing membranous disease. In contrast, it could be hypothesized that the immune process in one organ leads to exposures of certain antigens and possibly formation of antibodies for antigens in other organs.²⁴ Other groups identified other antibodies that could be involved in disease pathogenicity or possibly develop subsequent to the primary insult.²⁵ It seems that several antibodies can participate in the pathogenesis of MN.²⁴

Plasma exchange has been an effective standard of care for the treatment of TTP. Because relapse of disease can be life threatening, preventing relapse is a critical component of management. Patients with low ADAMTS13 factor activity have a high risk of relapse, and thus ADAMTS13 factor activity and inhibitor level are useful markers in predicting relapse. Rituximab has been increasingly used to prevent relapses in TTP²⁶ and as an effective immunosuppressive agent in MN.^{27–29} There were 2 reported cases of successful treatment of TTP and MN with rituximab, before the era of PLA2R monitoring.^{30,31} It is unfortunate that our patient was lost to follow-up, and that we could not assess any potential response to anti-B-cell therapy.

CONCLUSION

Severe proteinuria in the setting of TTP should prompt a search for a secondary etiology. Although evidence to support a direct relationship between TTP and MN is lacking, it is possible that the same process that caused ADAMTS13 deficiency also resulted in immune complex deposition in the kidney. Presentations of concurrent autoimmune diseases continue to enrich our understanding of disease pathogenicity. Rituximab is a promising agent for targeting different autoimmune conditions that may share a primary etiology. Disease registries for uncommon conditions such as TTP and MN may be useful to enhance research into pathogenesis.

DISCLOSURE

All the authors declared no competing interests.

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