ORIGINAL ARTICLE

A retrospective review of antiphospholipid syndrome: a single tertiary centre experience

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ABSTRACT

Introduction: Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterised by thrombosis and pregnancy morbidity in the presence of antiphospholipid antibodies (aPL). Our study aims to study the clinical and laboratory characteristics, treatment strategies and outcomes of APS patients retrospectively.

Materials and Methods: A retrospective review of all APS patients treated in Rheumatology Unit, Hospital Pulau Pinang between October 2021 and October 2022 was conducted.

Results: A total of 53 APS patients (age 42.4±13.9 years) including 22 (41.5%) primary and 31 (58.5%) secondary APS patients were identified. Thrombosis was the most common clinical manifestation (51/53; 96.2%) followed by pregnancy morbidity (15/45; 33.3%). For other clinical manifestations, aPL-associated thrombocytopenia was the most frequently observed manifestation (26.4%) followed by autoimmune haemolytic anaemia (18.9%). Lupus anticoagulant (LA) (88.7%) was the most commonly found aPL followed by anticardiolipin antibody (aCL) (50.9%) and anti-beta 2 glycoprotein 1 antibody (B2GP1) (30.2%). 10 (18.9%) patients tested positive for all three aPL. The majority of our patients (86.8%) receive warfarin as anticoagulation therapy while the remaining receive aspirin or direct oral anticoagulants.

Conclusion: Our population cohort demonstrated a high incidence of pregnancy morbidities and a similar incidence of thrombotic events compared to other population cohorts in both Asian and the European countries.

KEYWORDS:
Antiphospholipid syndrome, antiphospholipid antibodies, pregnancy morbidity, thrombosis, systemic lupus erythematosus

INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterised by vascular thrombosis and pregnancy morbidity in the presence of antiphospholipid antibodies (aPL).[1] This condition is characterised as primary when it occurs alone and secondary when it is associated with other autoimmune diseases, such as systemic lupus erythematosus (SLE).[2]

Patients with APS can present with a variety of clinical, haematological and serological manifestations. Apart from thrombosis and obstetric morbidities, other features, also known as non-criteria manifestations of APS have been shown to be associated with APS. These features include immune thrombocytopenia and autoimmune haemolytic anaemia, livedo reticularis, Libman-Sachs endocarditis, APS nephropathy and cognitive dysfunction.[3] Although these non-criteria manifestations are not specific to primary APS, studies have suggested that their presence could potentially be associated with an increased risk of thrombosis.[4]

Although rare, another subgroup of APS patients can develop catastrophic antiphospholipid syndrome (CAPS), which is characterised by widespread thromboses with end organ damage and is associated with a significantly higher degree of mortality.[5]

Determining the prevalence of APS remains challenging due to changes in the definition of APS classification criteria, the lack of standardisation to detect aPL, differences in laboratory cutoffs and difficulties in confirming aPL positivity 12 weeks after the initial measurement. Fortunately, several new publications in the recent years have greatly improved our insights on the incidence and prevalence of APS.

In the United States, the estimated population prevalence of APS is 50 cases per 100,000 with an annual incidence of 2.1 per 100,000.[6] In the United Kingdom, the estimated population prevalence of APS is 43 per 100,000 with an annual incidence of 1.8 per 100,000.[7] In Spain, the estimated population prevalence of APS is 40 cases per 100,000.[8] In the Asian population, the estimated population prevalence of APS is six cases per 100,000 with an annual incidence of 0.75 per 100,000.[9] CAPS have been estimated to affect less than 1% of patients with APS.[10]

Observational studies have shown that aPL may be positive in as many as 13% of patients with stroke, 11% of patients with myocardial infarction and 9.5% of patients with deep vein thrombosis.[11] aPL can be present in normal healthy population as well but the data on the prevalence of aPL among healthy population is still limited. In addition, other autoantibodies such as IgA isotypes (IgA anticardiolipin antibodies and IgA anti-beta 2 glycoprotein 1 antibodies), and phosphatidylserine/prothrombin complex autoantibodies (aPS/PT), among others, have also been reported to cause APS but their clinical relevance remains controversial.[12]

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Our study aims to describe the clinical features, serological characteristics, treatment strategies and outcomes of APS patients treated at Rheumatology Unit, Hospital Pulau Pinang, Malaysia.

MATERIALS AND METHODS

This was a retrospective cross-sectional study of patients with APS treated in Rheumatology Unit, Hospital Pulau Pinang from October 2021 until October 2022.

The diagnosis of APS was made according to the Sapporo's classification criteria in 2006 where patients must fulfil at least one clinical and one laboratory criteria (Table I).[3]

Demographic data, types of APS, clinical manifestations, treatment strategies, serological features and treatment outcomes were retrieved from medical records.

Data was analysed using Statistical Package for Social Sciences Software (version 21.0). Numeric variables were expressed as mean ± standard deviation and categorical variables were expressed as numbers and percentage. Mann-Whitney test was used to compare differences between two independent groups if the distribution were not normal. $p<0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Of the 53 adult patients with APS, eight (15.1%) were males and 45 (84.9%) were females, with a mean age of 42.4±13.9 years. Majority of the APS patients were Malays (23/53, 43.4%), followed by Chinese (17/53, 32.1%) and Indians (13/53, 24.5%). Twenty-two (41.5%) have primary APS while 31 (58.5%) have secondary APS. Out of the 31 patients with Secondary APS, 30 had SLE while the remaining one had Takayasu's arteritis. The mean age of onset of APS in was 32.6±12.4 years (Table II).

Clinical Manifestations

A total of 26 (49.1%) patients developed venous thrombosis while 30 (56.6%) had arterial thrombosis. Six (11.3%) patients developed both arterial and venous thrombosis. Of all the patients with venous thrombosis, 21 (39.6%) had deep vein thrombosis while eight (15.1%) had pulmonary embolism. Other APS patients who developed venous thrombosis had cerebral venous thrombosis (3/53, 5.7%), retinal vein thrombosis (1/53, 1.9%) and Budd-Chiari Syndrome (1/53, 1.9%). Of all patients with arterial thrombosis, 17 (32.1%) had ischaemic stroke while 7 (13.2%) had digital ischaemia. The remaining patients with arterial thrombosis had intracardiac thrombus (2/53, 3.8%), coronary artery disease (1/53, 1.9%) and small artery thromboses (1/53, 1.9%) (Table III).

Another 15 (33.3%) patients had pregnancy morbidities where four patients experienced early foetal loss and five patients experienced late foetal loss. Three patients had premature births and pre-eclampsia respectively (Table III).

Fourteen (26.4%) patients had thrombocytopenia where nine of these patients have concomitant SLE while the remaining five are patients with primary APS. Ten (18.9%) patients had autoimmune haemolytic anaemia, where nine had concomitant SLE and the remaining one was a patient with primary APS. Only one patient had valvular heart disease, APS nephropathy, epilepsy and vasculitic ulcer respectively while another two had livedo reticularis. None of our patients develop cognitive dysfunction (Table III).

Serological Characteristics

Ten (18.9%) patients tested positive for all three aPL while 17 (32.1%) patients tested positive for at least two aPL and 26 (49.1%) patients tested positive for only one of the aPL. Forty-seven (88.7%) patients tested positive for lupus anticoagulant (LA) while 27 (50.9%) patients and 16 (30.2%) patients tested positive for aCL and anti-beta 2 glycoprotein 1 antibody (B2GP1) respectively. Thirty-seven (69.8%) patients had antinuclear antibodies (ANA), of which seven were primary APS patients and 30 were secondary APS patients. Seventeen (32.1%) patients had anti-double stranded DNA (dsDNA) and all these patients were patients with SLE. All primary APS patients who tested positive for ANA tested negative for anti-dsDNA. Nine (17%) of APS patients tested positive for anti-SSa while three (5.67%), five (9.4%) and six (11.3%) tested positive for anti-SSb, anti-Sm and anti-RNP respectively. 21 (43.4%) of our APS patients had low complement levels, of which 21 were SLE patients while the remaining two patients were patients with primary APS (Table III).

Treatment Decisions

Forty-six (86.8%) patients received warfarin while 10 (18.9%) received aspirin for treatment of APS. Only two (3.8%) of our APS patients received direct oral anticoagulants (Table IV).

Follow up Duration and Treatment Outcomes

The mean follow-up duration of APS patients in our population were 13±6 years. Fifty-two (98.1%) patients are alive while one (1.9%) patient passed away due to advanced cervical carcinoma (Table IV).

Differences Among Primary and Secondary APS Patients
Demographics

In our population cohort, both primary and secondary APS patients were more prevalent among females (14.3 vs. 85.7%, 15.6 vs. 84.4%). More patients with secondary APS had an age at onset of less than 20 years of age compared to primary APS patients (18.8 vs. 4.8%). More secondary APS patients also had an age at onset of more than 50 years old compared to primary APS patients (9.4 vs. 4.8%). However, we could not demonstrate a statistical significance when comparing the prevalence of primary or secondary APS patients in relation to the age of onset (Table V).

Clinical Manifestations

In our study population, more patients with secondary APS had arthritis, rash and ulcers and AIHA. Both primary and secondary APS patients have similar incidence of thrombocytopenia, venous thrombosis, arterial thrombosis, and pregnancy morbidities (Table V).

Table I: Sapporo classification criteria for antiphospholipid syndrome.

Clinical criteria	
1. Vascular thrombosis (confirmed by imaging or histopathological studies) 2. Pregnancy morbidity	a. One of more clinical episodes of arterial, venous or small vessel thrombosis, in any tissue or organ. a. Three or more sequential spontaneous abortions before 10th week of gestation; or b. Unexplained foetal death of a morphologically normal foetus after 10th week of gestation; or c. Early birth before 34th week of gestation of a morphologically normal foetus due to eclampsia, severe pre-eclampsia or confirmed placental failure
Laboratory criteria	
	a. Lupus anticoagulant present in plasma, confirmed on minimally two occasions with an interval of at least 12 weeks b. Anticardiolipin-antibodies (aCL), IgG- or IgM- isotype, present in serum or plasma, with elevated titre (>99th percentile), confirmed on minimally two occasions with an interval of at least 12 weeks c. Anti-beta 2 glycoprotein-1-antibodies (B2GP1), IgG- or IgM-isotype, present in serum or plasma (with titre >99th percentile), confirmed on minimally two occasions with an interval of at least 12 weeks

Table II: Demographic data of APS patients.

Characteristics	**Value**
Mean age (years) (±SD)	42.4±13.9
Gender	
Male, n(%)	8 (15.1%)
Female, n(%)	45 (84.9%)
Ethnic	
Malay, n(%)	23 (43.4%)
Chinese, n(%)	17 (32.1%)
Indian, n(%)	13 (24.5%)
Types of APS	
Primary APS, n(%)	22 (41.5%)
Secondary APS, n(%)	31 (58.5%)
Mean age at diagnosis (years) (±SD)	32.6 ± 12.4

Serological Characteristics

While more primary APS patients tested positive for LA (95.5 vs. 83.8%, p=0.19), and more secondary APS patients tested positive for ACL (54.8 vs. 45.5%, p=0.50) and B2GP1 (35.5 vs. 22.7%, p=0.32), the differences were not statistically significant. In our population cohort, secondary APS patients with triple positivity were much higher compared to primary APS patients (19.4 vs. 18.2%, p=0.04). However, we did not observe any statistical significance when comparing patients who tested positive for only two aPL among the primary and secondary APS patients. ANA positivity was found in majority of our secondary APS patients (96.8 vs. 31.8%, p=0.002). Anti-double stranded DNA (DsDNA) was also present in significantly more secondary APS patients compared to primary APS patients. More secondary APS patients in our population tested positive for extractable nuclear antigens, namely anti-Ro, anti-La, Anti Sm and anti-RNP (Table V).

DISCUSSION

In this study, we report a retrospective observation of APS patients in Hospital Pulau Pinang, Malaysia. The mean age of APS patients in our study was below 50 years (mean age of onset of APS 32.6±12.4 years) which was similar to other population studies.6 Interestingly, the frequency of secondary APS was higher in our study population compared to primary APS. This finding was similar to another study from Singapore[13] but different compared to the European, American, French and the Euro-Phospholipid cohort.[15] A recent retrospective study from Pakistan also showed a higher incidence of primary APS compared to secondary APS in their population cohort (88 vs. 12%).[16] This may be due to a lack of awareness to screen young patients who present with thrombotic events and pregnancy morbidities in our region, leading to a lower detection rate of primary APS.

In our study population, patients with APS have a male to female ratio of 1:5.5. This finding is consistent with the fact that systemic autoimmune diseases, including SLE and APS tend to be more frequent in women.[17]

All our secondary APS patients have SLE, except for one patient who was diagnosed with Takayasu arteritis with secondary APS. The incidence of Takayasu arteritis and secondary APS remains largely unknown. To date, there has only been one case report detailing a patient who was diagnosed with Takayasu's arteritis and secondary APS.[18] It is postulated that high titres of antiphosholipid antibodies may trigger large-vessel vasculitis in secondary APS.[18] In addition to SLE, Mushtaq et al also reported cases of rheumatoid arthritis, ANCA associated vasculitis and mixed connective tissue disease being associated with secondary APS.[16]

In our retrospective study, approximately one third of our female APS patients experienced pregnancy morbidities. Another local study in Kelantan, Malaysia reported an even higher incidence of pregnancy morbidities (78.6%) among

Table III: Clinical manifestations and serological characteristics of APS patients.

Characteristics	Value
Venous thrombosis	26 (49.1)
Deep vein thrombosis	21 (39.6)
Pulmonary embolism	8 (15.1)
Cerebral venous thrombosis	3 (5.7)
Retinal vein occlusion	1 (1.9)
Budd-Chairi syndrome	1 (1.9)
Arterial thrombosis	30 (56.6)
Cerebrovascular accident	17 (32.1)
Digital ischaemia	7 (13.2)
Coronary artery disease	1 (1.9)
LV thrombus	2 (3.8)
Iliac artery thrombosis	1 (1.9)
Mesenteric artery thrombosis	1 (1.9)
Renal artery thrombosis	1 (1.9)
Arterial and venous thrombosis	6 (11.3)
Pregnancy morbidities	15 (33.3)
Early foetal loss	4 (26.7)
Late foetal loss	5 (33.3)
Early and late foetal loss	5 (33.3)
Premature birth	3 (20.0)
Pre-elcampsia/eclampsia	3 (20.0)
Valve disease	1 (1.9)
APS nephropathy	1 (1.9)
Livedo Reticularis	2 (3.8)
Cognitive dysfunction	0
Thrombocytopenia	14 (26.4)
Epilepsy	1 (1.9)
Autoimmune haemolytic anaemia	10 (18.9)
Vasculitic ulcer	1 (1.9)
Serological Characteristics	**Value, n (%)**
Lupus anticoagulant	47 (88.7)
Anti-cardiolipin antibody	27 (50.9)
Anti-beta 2 glycoprotein 1 antibody	16 (30.2)
Single positive	26 (49.1)
LA 24 (92.3)	
aCL	2 (7.7)
B2GP1	0
Double positive	17 (32.1)
LA + aCL	11 (64.7)
LA + B2GP1	2 (11.8)
aCL + B2GP1	4 (23.5)
Triple positive	10 (18.9)
Antinuclear antibody (ANA)	37 (69.8)
Anti-double stranded DNA (Anti-dsDNA)	17 (32.1)
Extractable nuclear antigen (ENA)	
Anti-SSa	9 (17)
Anti-SSb	3 (5.67)
Anti-Sm	5 (9.4)
Anti-RNP	6 (11.32)
Low complements (C3 and C4)	23 (43.4)

Table IV: Treatment and Outcomes of APS patients.

Treatment	Value, n (%)
Warfarin	46 (86.8)
Aspirin	10 (18.9)
Direct oral anticoagulants	2 (3.8)
Treatment Outcome	**Value, n (%)**
Alive	52 (98.1)
Dead	1 (1.9)

Table V: Differences in demographics, clinical manifestations and serological characteristics among primary and secondary APS patients.

	Primary APS n=22	Secondary APS n=31	p value
Demographics			
Male, n(%)	3 (14.3)	5 (15.6)	0.80
Female, n(%)	18 (85.7)	27 (84.4)	0.80
Age at onset less than 20 years old, n(%)	1 (4.8)	6 (18.8)	0.14
Age at onset more than 50 years old, n(%)	1 (4.8)	3 (9.4)	0.53
Clinical manifestations			
Arthritis, n (%)	0 (0)	11 (35.5)	0.002
Mucocutaneous – rash and ulcer, n (%)	1 (4.5)	12 (38.7)	0.004
Renal involvement, n (%)	1 (4.5)	0	0.21
Livedo reticularis, n (%)	0 (0)	2 (6.5)	0.22
AIHA, n (%)	1 (4.5)	9 (29.0)	0.02
Thrombocytopenia, n (%)	5 (22.7)	9 (29.0)	0.61
Venous thrombosis, n (%)	9 (40.9)	11 (35.5)	0.69
Arterial thrombosis, n (%)	8 (36.4)	17 (54.8)	0.18
Both venous and arterial thrombosis, n (%)	3 (13.6)	3 (9.7)	0.65
Pregnancy morbidities, n (%)	6 (27.3)	9 (29.0)	0.89
Pregnancy morbidity and thrombosis	5 (22.7)	8 (25.8)	0.79
Serological characteristics			
LA, n (%)	21 (95.5)	26 (83.8)	0.19
aCL, n (%)	10 (45.5)	17 (54.8)	0.50
B2GP1, n (%)	5 (22.7)	11 (35.5)	0.32
Double positivity, n (%)	6 (27.3)	11 (35.5)	0.66
Triple positivity, n (%)	4 (18.2)	6 (19.4)	0.04
ANA, n (%)	7 (31.8)	30 (96.8)	0.002
dsDNA, n (%)	0	17 (54.8)	0.005
Anti-SSA, n (%)	0	9 (29.0)	0.007
Anti-SSB, n (%)	0	3 (9.7)	0.15
Anti-Sm, n (%)	1 (4.5)	3 (9.7)	0.53
Anti-RNP, n (%)	0	6 (19.4)	0.04

female APS patients while a retrospective study of an Italian cohort reported a lower incidence of pregnancy morbidities among female APS patients (12.4%).[10,19] Late foetal demise was the most common obstetric manifestation in our study, similar to studies from Thailand and Japan.[20,21] Interestingly, we did not observe any difference in the incidence of pregnancy morbidities between our primary APS and secondary APS patients.

In our cohort, DVT was the major thrombotic event. DVT was the most common venous thrombotic event while cerebral infarction was the most common arterial thrombotic event. The incidence of venous thrombosis reported in our study was slightly lower compared to arterial thrombosis (49.1 vs. 56.6%). This was different from findings reported in another retrospective study of Hungarian APS patients where the incidence of venous thrombosis was higher (36.4%) compared to arterial thrombosis (33.8%).[22] Compared to the Euro-Phospholipid project, our population cohort had a similar incidence of deep vein thrombosis (39.6 vs. 38.69%) and pulmonary embolism (15.1 vs. 14.1%) but a higher incidence of ischaemic stroke (32.1 vs. 19.8%).[23]

Catastrophic APS, a rare and feared complication of APS which usually occurs in less than 1% of patients with APS was not reported in our cohort of patients.

In our cohort, LA was the most common aPL detected, followed by aCL and B-2 glycoprotein-I antibody. This was different compared to the Euro-Phospholipid Project and Pakistan cohort where aCL antibodies was the most common antibody found in their cohort of primary and secondary APS patients.[16,23] Out of the eleven patients who tested positive for both LA and aCL, five patients (45.5%) developed thrombotic events only while six patients (54.5%) developed both thrombotic events and pregnancy morbidities. Out of the four patients who tested positive for LA and B2GP1, three patients (75%) developed thrombotic events while one patient (25%) developed both thrombotic events and pregnancy morbidities. This finding indicates that the presence of LA poses a higher risk of developing thrombotic events compared to pregnancy morbidities. This is consistent with previous studies showing that the presence of LA has an odds ratio for thrombosis 5 to 16 times higher than controls.[22]

Additionally, several APS-related manifestations which were not included in the classification criteria were also found in our population cohort. In our study, APS-associated thrombocytopenia is one of the most common non-criterion manifestations of APS (26.4%) followed by AIHA (18.9%). The incidence of APS-associated thrombocytopenia in our study population was comparable to the Euro-Phospholipid project (29.6%) while our incidence of AIHA was significantly higher compared to the Euro-Phospholipid project (9.7%).23 Compared to our study population, the Singapore cohort has a higher incidence of APS-associated thrombocytopenia (49.2%) and a similar incidence of AIHA (22%).[13]

In our study cohort, only one patient (1.9%) developed epilepsy, vasculitic skin ulcer and Libman-Sacks endocarditis

respectively which was slightly lower than what was being reported from the Euro-Phospholipid project.[23] Compared to the Euro-Phospholipid project, we also had lower incidence of livedo reticularis being reported (3.8 vs. 24.1%).[23]

Interestingly, there was one patient in our population cohort that was diagnosed with Evans syndrome a few years after the diagnosis of primary APS. To date, there has only been one case report on simultaneous Evans syndrome and primary APS.[24]

APS nephropathy has previously been reported to affect approximately 2.7% of APS patients.[25] In our population cohort, only one patient (1.9%) had APS nephropathy evidenced by presence of renal artery thrombosis. However, the true incidence of renal involvement in APS is likely higher as renal biopsies are often not performed due to the use of anticoagulant therapy, thrombocytopenia, systemic hypertension and concerns of biopsy-related complications.[26] Among other features, 60% (18/30) of our APS patients with SLE also presented with lupus nephritis in our study. None of our APS patients developed catastrophic APS.

The presence of secondary APS in SLE patients has been shown to significantly affect survival and outcomes of these patients. Pons-Estel et al. demonstrated that eight-year survival of primary APS patients is 83% while patients with SLE and secondary APS had survival rates of 75%.[27] The Euro-Phospholipid Project, on the other hand, demonstrated a similar mortality rate among primary APS patients and secondary APS patients with SLE (7.1 vs. 6.8%).[23] In our cohort, only one secondary APS patient with SLE passed away after a mean follow up of 8 years due to advanced cervical carcinoma. The observed reduced mortality in our cohort can be explained by the fact that our cohort had fewer patients compared to other population cohort from other parts of the world.

A substantial number of our patients (86.8%) received warfarin while only 18.9% and 3.8% received aspirin and DOAC respectively for treatment of APS. Vitamin K antagonist (VKA) oral anticoagulants have always been the preferred pharmacological management of thrombotic APS. However, its use is accompanied by problems, such as the need for frequent blood taking for INR monitoring, drug and food interaction and teratogenicity. Novel direct oral anticoagulant (NDOAC), including direct oral thrombin inhibitor (e.g., dabigatran) and direct anti-Xa inhibitors (e.g., rivaroxaban, apixaban and edoxaban) may be effective in the prevention of thrombosis in APS patients. Cohen et al showed that rivaroxaban could be a safe and effective alternative treatment in APS patients as there was no observed difference in thrombotic events of major bleeding during the six-month follow up.[28] However, the significantly shorter half-life of DOACs may lead to a higher recurrent thrombotic risk compared to VKA. Hence, switching from VKA to DOACs in patients with poor compliance to VKA is not appropriate or recommended.[29] In our population cohort, two thrombotic APS patients who received rivaroxaban have not developed any recurrent thrombotic events.

There are some limitations to this study. Firstly, our study was a retrospective study, and the sample size was relatively smaller compared to other population cohort. Furthermore, the true prevalence of APS may be underestimated as non-criteria manifestations of APS, including autoimmune haemolytic anaemia, APS nephropathy, cognitive dysfunction, livedo reticularis and Libman-Sachs endocarditis have been shown to be associated with APS more recently.

CONCLUSION

In conclusion, antiphospholipid syndrome (APS) is a complex thromboinflammatory syndrome with various clinical manifestations. Our population cohort demonstrated a high incidence of pregnancy morbidities as well as a similar incidence of thrombotic events when compared to other population cohorts in both Asian and European countries. Most of our APS patients with thrombotic events receive warfarin. The epidemiology of APS remains limited as larger population-based studies are needed to determine the frequency of APS among different racial and ethnic groups. As the classification criteria for APS continues to evolve, more patients may be reclassified as APS patients in the future. Hence, the incidence and prevalence of APS may continue to evolve in the future.

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CONFLICT OF INTEREST

No conflict of interest declared.

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