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ORIGINAL ARTICLE

A 15-year single centre retrospective study of antiphospholipid syndrome patients from Northern Malaysia

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Abstract

Background: Antiphospholipid syndrome (APS) is an autoimmune disorder characterised by thrombosis and/or pregnancy morbidity in the presence of antiphospholipid antibodies (aPLs) based on the Sydney criteria. We aimed to explore the clinico-laboratory features and treatment strategies of APS patients retrospectively. *Methodology:* The medical records of APS patients registered under Hospital Universiti Sains Malaysia (Kelantan state) between 2000 and 2015 were reviewed. *Results*: A total of 17 APS subjects (age 40.7 ± 12.8 years) including 11 primary (64.7%) and six secondary APS (35.3%) patients were identified. The follow-up period was 9.5 ± 6.7 years with male:female ratio of 1.0:4.7. Pregnancy morbidity was the most common clinical manifestation (11/14; 78.6%) followed by recurrent venous thrombosis (10/17; 58.8%). For other clinical features, menorrhagia was the most frequently observed manifestation (4/14; 28.6%) followed by aPLs-associated thrombocytopenia (4/17; 23.5%) and ovarian cyst (3/14; 21.4%). LA and aCL were positive in 94.1% (16/17) and 81.8% (9/11) of the patients, respectively. APTT value (76.7 ± 17.0 sec) was significantly high ($p < 0.05$). Low intensity warfarin alone was successful to maintain target INR (2.0 - 3.0) and prevent recurrence of thrombosis. *Conclusion*: The tendency of pregnancy morbidity in this cohort of Malaysian Kelantanese APS patients was high compared to other previously reported APS cohorts. Low intensity warfarin was successful in preventing recurrence of thrombosis, however, APS women receiving long-term anticoagulants should be monitored for possible occurrence of menorrhagia and ovarian cysts.

Keywords: antiphospholipid syndrome, antiphospholipid antibodies, pregnancy morbidity, menorrhagia, ovarian cyst, anticoagulants, retrospective study

INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterised by the presence of vascular thrombosis (venous and/or arterial) and/or pregnancy morbidity besides the presence of serum antiphospholipid antibodies (aPLs) based on the latest Sydney classification criteria of definite APS.[1] According to the criteria, lupus anticoagulant (LA), anticardiolipin (aCL) and anti-β2-glycoprotein I (β2GPI) antibodies are included as laboratory features.

APS is classified into primary APS (PAPS: at least one clinical and one laboratory feature is present without the presence of any underlying autoimmune diseases),[2] secondary APS [SAPS: in addition to the clinical and laboratory features of APS, at least an autoimmune disease is present, mostly systemic lupus erythematosus (SLE)][3] and catastrophic APS (CAPS: the most aggressive form of APS which may result in multiple organ failure).[4] The prevalence of APS is 40 to 50 cases per 100,000 persons per year, and the incidence is estimated to be around five new cases per 100,000 persons per year.[5] Although, the optimal treatment for APS remains unclear, current regimens for thrombotic management

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of APS encompass: (i) anticoagulants (*i.e.,* warfarin); (ii) antiplatelet agents (*i.e.,* aspirin or clopidogrel) and (3) low molecular weight heparin (LMWH).[6] With proper management, 70% of the pregnant women with APS can deliver viable live infants.[7] According to a systematic review with meta-analysis,[8] unfractionated heparin along with aspirin provides a significant benefit in live births while the efficacy of LMWH plus aspirin remains obscure.

Although several APS-associated experimental studies and case reports have been reported from Southeast Asian countries including Indonesia,[9] Philippines,[10] Malaysia,[11] Thailand[12] and Singapore;[13] to the best of our knowledge, there is no comprehensive retrospective analysis on Malaysian patients with APS. This study aims to present a 15-year retrospective analysis on the clinico-laboratory features along with the treatment strategies received by a cohort of Malaysian Kelantanese APS patients.

MATERIALS AND METHODS

Data acquisition

Ethical approval was obtained from the Universiti Sains Malaysia (USM) Human Research Ethics Committee [USM/JEPeM16060217] and a written permission was acquired from the director of Hospital USM (HUSM) to review the patients' medical records. A list of 24 patients registered under different departments as 'probable APS' was identified from the online database of HUSM record unit between the year 2000 and 2015. All 24 medical records (including the clinical records, online laboratory and prescription databases) of the Malaysian Kelantanese patients as well as their follow-up disease duration were reviewed, ranging between one to 25 years (since 1990).

Retrospectively, their clinical records including features associated with APS, SLE and the presence of other autoimmune diseases or other clinical presentations were investigated from each patient's medical record. Laboratory characteristics consisting of haematological parameters [activated partial thromboplastin time (APTT) and platelet count (PLT)] and immunological parameters [LA, aCL, anti-β2GPI, anti-nuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA) and complement 3, 4 (C3, C4)] were retrieved.

In this retrospective report, the laboratory results were presented based on a total number of 843 tests [751 haematological (APTT, n = 469 and PLT, n = 282)] and 92 immunological tests associated with APS (LA and aCL) or SLE (ANA, anti-dsDNA and C3, C4). The current medication status of the confirmed APS patients was obtained from the online prescription database followed by cross-checking with the patients' medical record folder. The confirmation of APS and SLE was based on the APS[14] and SLE classification criteria.[15]

Statistical analysis

Mean ± standard deviation (SD) or percentages were calculated where applicable. Chi-square (Fisher's exact) test was performed to investigate the associations between the clinical, laboratory or immunological categorical data with the types of APS (PAPS and SAPS) and gender. Normally distributed variables were considered for 'Independent samples *t*-test' (age and PLT) and 'one-sample *t*-test' (APTT). All data analysis was performed using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinico-demographic characteristics

From the probable 24 APS patients, 17 patients were confirmed to have either PAPS (11/17; 64.7%) or SAPS (6/17; 35.3%) based on the 1999 Sapporo classification criteria.[14] None of the patients complied with the CAPS classification criteria.[5] All of the patients were of Malay ethnicity (mean age of 40.7 ± 12.8 years) including 14 females and three males (male:female ratio of 1.0:4.7). The 17 APS patients were followed up for an average of 9.5 ± 6.7 years at HUSM. Among them, four patients died due to multiple organ failure, severe bleeding or massive cerebral arterial infarction, while another four patients defaulted from follow-up at HUSM (Table 1).

Among the clinical criteria stated in the Sydney classification criteria of APS (Table 2), pregnancy morbidity showed the highest frequency (11/14; 78.6%) followed by venous thrombosis (10/17; 58.8%) (Fig. 1A).

Among other clinical features, menorrhagia was observed in 28.6% (4/14) of the patients followed by aPLs-associated thrombocytopenia (4/17; 23.5%), ovarian cyst (3/14; 21.4%), lupus nephritis (3/17; 17.6%), dyslipidaemia (2/17; 11.8%), preeclampsia (1/14; 7.1%), sepsis (1/17; 5.9%) and epilepsy (1/17; 5.9%) (Fig. 1B). Among the SAPS patients (n = 6), SLE alone was associated with three patients, Evan's

TABLE 1: Demographic data of patients with APS from HUSM

Patient no.	Age (years)	Sex	APS type	Follow-up duration
1	20	F	PAPS	8 years (2007– ongoing)
2	38	F	PAPS	16 years (2000 – ongoing)
3	49	F	PAPS	25 years (1990 – 2015) Died in 2015 because of multiple organ failure
4	30	F	PAPS	3 years (2011 – 2014)*
5	30	F	SAPS	9 years (2006 – ongoing)
6	29	F	PAPS	5 years (2001 – 2006)*
7	53	F	SAPS	11 years (2004 – ongoing)
8	41	F	PAPS	7 years (2003 – 2010) Died in 2010 because of multiple organ failure
9	41	F	SAPS	21 years (1994 – ongoing)
10	58	M	PAPS	8 years (2005 – 2013)*
11	69	M	PAPS	1.5 months (13th March, 2014 – 27th April, 2014)*
12	32	F	SAPS	10 years (2005 – ongoing)
13	46	F	PAPS	15 years (1997 – 2012)*
14	32	F	SAPS	5 years (2008 – 2013) Died in 2013 due to upper gastrointestinal bleeding
15	35	F	PAPS	11 years (2004 – ongoing)
16	56	M	PAPS	1 month (May, 2015 – June, 2015) Died in 2015 due to massive left middle cerebral artery infarction
17	33	F	SAPS	7 years (2008 – ongoing)

F: Female; M: Male; APS: Antiphospholipid syndrome; PAPS: Primary antiphospholipid syndrome; SAPS: Secondary antiphospholipid syndrome

*Patients stopped follow-up

syndrome was found in two patients while the co-occurrence of both SLE and Evan's syndrome were seen in one patient (Table 2).

Immunological and haematological features

Immunological tests revealed that most APS patients (16/17; 94.1%) were LA positive (undetermined in a single patient), whereas nine of 11 aCL positive subjects (81.8%) exhibited high titer of IgG aCL (118.8 ± 128.0 GPL). Nevertheless, IgG and IgM aCL values of another two patients were within the normal range (<40 GPL/MPL) (Table 3) and undetermined in six patients. ANA was present in 40% (6/15) of the APS patients, it was found more frequently in patients with SAPS (4/6; 66.7%). Anti-dsDNA was observed positive in 25% (3/12) of APS patients which was also more frequently seen in SAPS (2/3; 66.7%) when compared to PAPS patients. Similarly, lower levels of C4 (<0.20 g/dL) was observed in all of the SAPS patients (Table 3).

APTT was prolonged in all APS patients in presence of positive LA (Table 3). The mean APTT value (76.7 ± 17.0 sec) of all patients was significantly higher ($p < 0.05$) than the standard value of healthy control (37.9 sec). The mean PLT value of 47.0% (8/17) APS patients was lower than 150 x 10^9/L and 29.4% (5/17) of the patients had mean PLT lower than 100 x 10^9/L. In addition, the mean PLT of all the APS patients was 161.2 x 10^9/L, indicating the tendency of developing aPLs-associated thrombocytopenia (Table 3).

Treatment strategies

Approximately 43% (6/14) of the APS patients received sole or dual anticoagulant treatment with different dosages of warfarin and clexane (LMWH). A small percentage (3/14; 21.4%) received sole antiplatelet drugs (aspirin and clopidogrel), while 14.3% (2/14) received a combination of antiplatelet and anticoagulants or immunosuppressive drugs (mycophenolate and

TABLE 2: Clinical classification criteria, manifestations and treatment status of APS patients

Patient no.	Clinical classification criteria[#]	SLE or other autoimmune diseases	Other clinical manifestations	Medications* (dosage)	INR (range)
1	• Left common femoral arterial thrombosis • DVT of right superficial femoral and popliteal vein • Venous thrombosis	None	• Menorrhagia	Warfarin sodium (2.5 mg, OD)	2.5 ± 1.4 (1.0 - 8.6)
2	• Recurrent pregnancy morbidity (twice)	None	• Severe preeclampsia	Aspirin (75 mg, OD), Clexane (60 mg, BD)	1.0 ± 0.0 (0.9 - 1.1)
3	• Recurrent pregnancy morbidity (nine times)	None	• Recurrent epilepsy	NA	1.1 ± 0.0 (1.0 - 1.1)
4	• Arterial thrombosis • Left leg DVT	None	• Ovarian cyst • aPLs-associated thrombocytopenia • Hepatomegaly	Warfarin sodium (6.0 mg, OD), Clexane (60 mg, BD)	1.3 ± 0.3 (0.9 - 2.0)
5	• Recurrent pregnancy morbidity (five times)	SLE	• Lupus nephritis	Aspirin (75 mg, OD)	1.1 ± 0.0 (0.9 - 1.3)
6	• Pregnancy morbidity (once) • Recurrent right and left leg DVT • Arterial thrombosis	None	• Ovarian cyst • Menorrhagia	Warfarin sodium (4.5 mg, OD)	2.5 ± 1.9 (1.2 - 7.4)
7	• Venous thrombosis	Evan's syndrome	• aPLs-associated thrombocytopenia • Ovarian cyst • Menorrhagia	Mycophenolate (500 mg, BD)	1.5 ± 0.5 (1.0 - 2.6)
8	• Pregnancy morbidity (once) • Venous thrombosis • Recurrent DVT of left leg • Multiple arterial thrombosisNone	None	• aPLs-associated thrombocytopenia	NA	2.0 ± 1.4 (0.8 - 7.9)
9	• Pregnancy morbidity (twice) • Arterial thrombosis	Evan's syndrome	• None	Azathioprine (50 mg, OD), Aspirin (75 mg, OD)	1.1 ± 0.1 (0.9 - 1.0)
10	• Recurrent DVT	None	• None	Warfarin sodium (4.5 mg, OD)	2.1 ± 0.7 (1.0 - 4.4)
11	• Recurrent DVT • Arterial thrombosis	None	• Dyslipidaemia	Warfarin (4 mg, OD)	3.4 ± 2.1 (1.4 - 7.2)
12	• Recurrent pregnancy morbidity (twice) • Recurrent DVT	i. SLE ii. Evan's syndrome	• None	Warfarin sodium (3 mg, OD)	2.4 ± 1.7 (1.0 - 9.8)
13	• Recurrent pregnancy morbidity (twice) • Recurrent DVT • Arterial thrombosis	None	• None	Warfarin sodium (4 mg, OD), Clopidogrel (75 mg, OD)	0.9 ± 0.0 (0.8 - 1.0)

Patient no.	Clinical classification criteria[#]	SLE or other autoimmune diseases	Other clinical manifestations	Medications* (dosage)	INR (range)
14	• Recurrent pregnancy morbidity (four times) • Arterial thrombosis	SLE	• Lupus nephritis • Menorrhagia • aPLs-associated thrombocytopenia	NA	1.2 ± 0.4 (0.9 - 2.4)
15	• Recurrent pregnancy morbidity (twice)	None	• None	Aspirin (150 mg, OD)	1.1 ± 0.2 (0.9 - 1.7)
16	• Arterial thrombosis	None	• Idiopathic thrombocytopenic purpura	NA	1.1 ± 0.0 (1.1 - 1.2)
17	• Recurrent pregnancy morbidity (thrice)	SLE	• Dyslipidaemia • Sepsis • Lupus nephritis	Aspirin (75 mg, OD)	1.0 ± 0.0 (0.9 - 1.1)

NA: Not applicable (patients died during follow-up period); OD: Once daily; BD: Bis (twice) daily; APS: Antiphospholipid syndrome; SLE: Systemic lupus erythematosus; DVT: Deep vein thrombosis; INR: International normalized ratio (provided as mean ± SD)
*Medications are listed based on patients' last follow-up record.
[#]Vascular thrombosis was confirmed via appropriate imaging studies

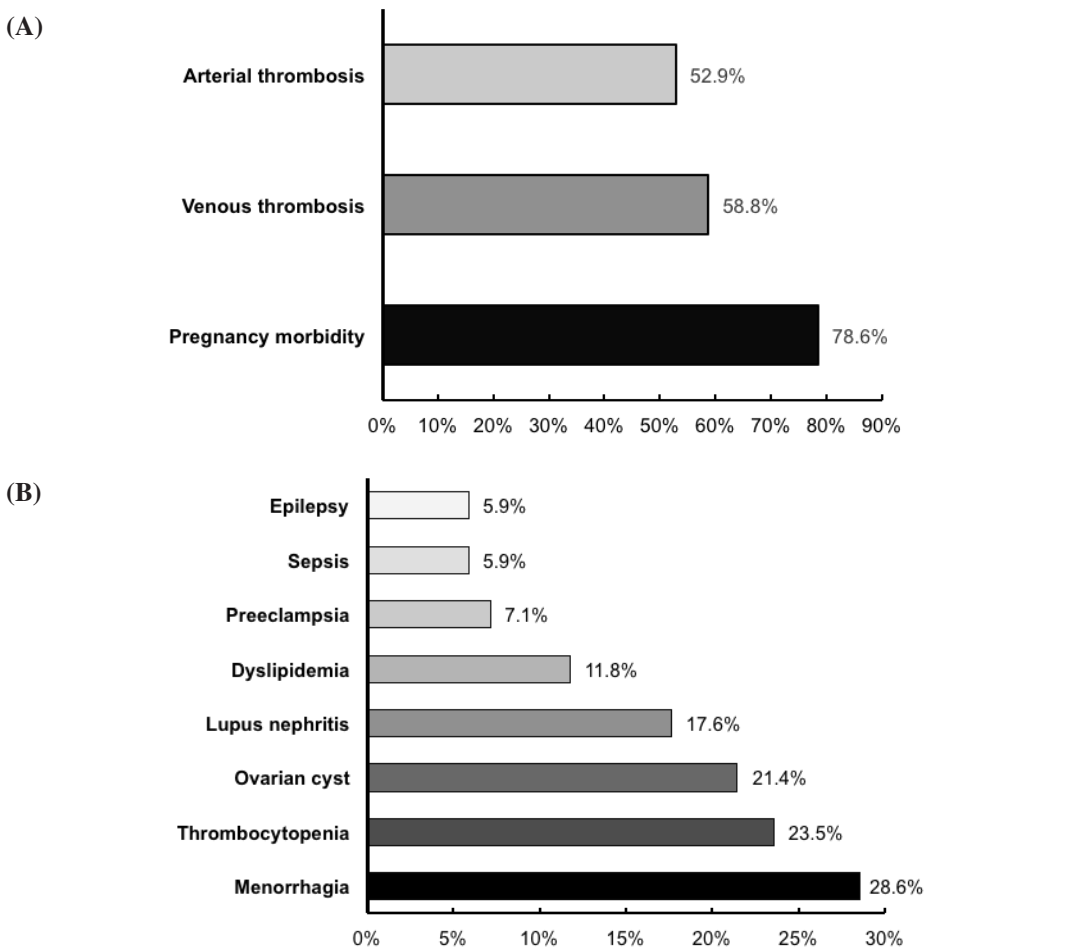

FIG. 1: (A) Clinical classification criteria and (B) other clinical manifestations observed in APS patients of HUSM (n = 17)

TABLE 3: Haematological and immunological markers of APS patients

Patient no.	APS-associated tests		SLE-associated tests			Haematological tests	
	LA	aCL (GPL/MPL)	ANA (titer)	Anti-dsDNA (titer)	C3, C4 (g/L)	APTT (sec)	Platelet (x 10^9/L)
1	+	IgG: 415.0 ± 37.0 IgM: 8.4 ± 1.9	-	-	1.06 ± 0.1, 0.21 ± 0.01	104.1 ± 23.0	225.1 ± 82.2
2	+	IgG: 157.0 ± 13.7 IgM: 3.5 ± 0.7	-	-	ND	81.3 ± 16.3	129.7 ± 28.5
3	+	ND	+ (1:80)	+	ND	54.3 ± 1.4	231.8 ± 30.0
4	+	IgG: 106.4 ± 7.5 IgM: 5.5 ± 0.3	-	-	ND	80.3 ± 12.3	65.7 ± 36.8
5	ND	IgG: 249.6 ± 144.3 IgM: 21.1 ± 7.4	+ (> 1:320)	+	0.40 ± 0.2, 0.04 ± 0.02	65.3 ± 23.2	135.2 ± 31.2
6	+	IgG: 3.7 ± 0.0 IgM: 4.1 ± 0.0	+ (1:80)	-	ND	71.0 ± 23.2	263.8 ± 25.5
7	+	ND	-	ND	0.67 ± 0.01, 0.07 ± 0.04	93.4 ± 42.7	55.1 ± 29.8
8	+	IgG: 35.9 ± 20.8 IgM: 4.3 ± 0.8	-	-	0.99 ± 0.00, 0.16 ± 0.00	85.3 ± 52.5	51.6 ± 51.9
9	+	IgG: 207.0 ± 0.0 IgM: 0.1 ± 0.0	+ (1:320)	-	0.73 ± 0.00, 0.10 ± 0.00	82.6 ± 17.6	248.4 ± 55.2
10	+	ND	-	ND	0.76 ± 0.03, 0.20 ± 0.02	67.6 ± 18.2	97.7 ± 41.9
11	+	ND	-	-	ND	72.0 ± 26.3	214.0 ± 0.0
12	+	ND	ND	ND	ND	109.2 ± 38.3	289.8 ± 33.5
13	+	IgG: 23.7 ± 0.0 IgM: 0.5 ± 0.0	-	-	1.53 ± 0.00, 0.36 ± 0.00	70.7 ± 60.6	214.3 ± 28.1

Patient no.	APS-associated tests		SLE-associated tests			Haematological tests	
	LA	aCL (GPL/MPL)	ANA (titer)	Anti-dsDNA (titer)	C3, C4 (g/L)	APTT (sec)	Platelet (x 10^9/L)
14	+	ND	+ (1:40)	+	0.41 ± 0.07, 0. 07 ± 0.04	62.6 ± 52.9	196.3 ± 45.2
15	+	IgG: 41.2 ± 15.6 IgM: 5.3 ± 0.8	ND	ND	ND	57.1 ± 18.8	117.6 ± 89.4
16	+	IgG: 47.4 ± 0.0 IgM: 4.3 ± 0.0	-	ND	ND	96.1 ± 5.4	18.3 ± 10.7
17	+	IgG: 21.1 ± 8.5 IgM: 41.6 ± 4.8	+ (1:320)	-	0.98 ± 0.16, 0.19 ± 0.05	50.7 ± 9.8	187.0 ± 30.1

APS: Antiphospholipid syndrome; SLE: Systemic lupus erythematosus; LA: Lupus anticoagulant; aCL: Anticardiolipin; ANA: Anti-nuclear antibody; dsDNA: Double - stranded DNA; C3, C4: Complement component 3, 4; IgG: Immunoglobulin G; IgM: Immunoglobulin M; ND: Not determined; '+': Positive; '-': Negative

azathioprine). When warfarin was used alone, it was a remarkable secondary prophylaxis in which all of the recurrent thrombotic APS patients (n = 5) were successfully managed and achieved target INR of between 2.0 and 3.0. Interestingly, combined treatment of anticoagulant and antiplatelet drugs failed to maintain the target INR in all of the three APS patients (Table 2). All of the four female APS patients with history of recurrent pregnancy morbidity (the only clinical manifestation without thrombotic events) were treated with aspirin alone or aspirin in combination with clexane during their pregnancies and subsequently, at least three of them delivered live infants (one patient not reported).

DISCUSSION

Demographic characteristics

In this study, we report the long-term retrospective observation (15 years) of APS patients from Malaysia as well as Southeast Asia. The mean age of the APS patients in this study was below 50 years (onset of APS 24.2 ± 5.4 years) which complies with previous findings where APS was reported to affect mostly young adults.[16,17]

The frequency of PAPS (11/17; 64.7%) was higher than that of SAPS (6/17; 35.3%) as also reported in similar retrospective studies on European cohort (n = 156; PAPS: 58.7%, SAPS: 41.3%),[18] American cohort (n = 61; PAPS: 57.3%, SAPS: 42.7%),[19] French cohort (n = 16; PAPS: 81.0%, SAPS: 19.0%)[20] and Euro-Phospholipid cohort (n = 1,000; PAPS: 53.1%, SAPS: 46.9%).[21]

Based on our retrospective study, the prevalence of female APS patients was clearly higher (14/17; 82.4%) than that of males (3/17; 17.6%) as also similarly reported by the Euro-Phospholipid cohort (n = 1,000) study where 82% of participants were females.[21] In the latest comprehensive review on autoimmune diseases,[22] globally the female predominance was also observed in patients with systemic autoimmune and rheumatologic diseases.

Clinical characteristics of the APS patients

Pregnancy morbidity is a well-recognised clinical presentation of APS[1] in which a persistently positive and high titer of aPLs increases the incidence of foetal loss in female patients with APS.[23,24] In our retrospective study, recurrent pregnancy morbidity was the most common clinical manifestations among 78.6% (11/14) of the female APS patients who had positive and

high titer of LA and IgG/IgM aCL antibodies. Similarly, pregnancy morbidities were also observed in other APS cohorts albeit at lower frequencies compared to our study [51% in an European multicentre clinical study (n = 116)[25] and 12.4% in a retrospective study (n = 97) of an Italian cohort].[26] These results suggest that Malaysian Kelantanese APS women tend to experience higher occurrence of pregnancy morbidities than European APS patients.

Thrombosis is another major clinical criterion of APS where venous thrombosis is most commonly observed.[27] The incidence of venous thrombosis reported in our study was higher (10/17; 58.8%) compared to arterial thrombosis (9/17; 52.9%). Similar findings were also reported in another retrospective study of Hungarian APS patients (n = 506) where the incidence of venous thrombosis was higher (36.4%) compared to arterial thrombosis (33.8%).[28] Eight of the APS patients showed both high titres of IgG aCL and positive LA (with prolonged APTT), the presence of which is considered as a risk factor of developing thrombi in patients with APS.[29,30] Interestingly, among these double positive (LA and aCL) APS patients, 62.5% (5/8) exhibited thrombotic events while 50% (4/8) showed recurrent pregnancy morbidities.

Other clinical characteristics of the APS patients

From the literature, few APS cases were observed with menorrhagia, although in APS patients menorrhagia is suspected because of norethisterone[31] and anticoagulants administration.[32] In fertile women (without APS), increased menorrhagia is observed also due to oral administration of anticoagulants.[33] In our cohort of APS patients experiencing menorrhagia, 3/4 were taking oral anticoagulants. Therefore, the cause of menorrhagia in APS patients might be due to anticoagulation-induced haemorrhage.

aPLs-associated thrombocytopenia is one of the most common haematological features of APS.[34] Although the association of thrombocytopenia with APS is recognised, this feature is not adopted as an independent criterion for definite APS diagnosis in the revised APS classification criteria.[1] In this study, aPLs-associated thrombocytopenia was observed in almost a quarter (23.5%; 4/17) of APS patients. Similarly, Euro-Phospholipid project demonstrated thrombocytopenia in 29.6% (296/1,000) of APS patients.[4] Another study conducted on Singaporean cohort reported higher frequency (49.2%; 29/59) of thrombocytopenia in definite APS patients.[13]

A thorough search of the relevant literature yielded only two reports[35,36] where six APS cases experienced ovarian cysts and another retrospective study reported one of 15 APS patients with ovarian cysts.[37] Due to long-term anticoagulation treatments, it was anticipated that the ovarian cysts were ruptured, causing the onset of ovarian cysts[35] and menorrhagia.[32] In our cohort, 2/3 APS patients were treated with oral anticoagulants due to which ovarian cysts might have ruptured leading to menorrhagia.

Among other features, 17.6% (3/17) of APS patients with SLE presented with lupus nephritis in our study. There are also several case reports where lupus nephritis was reported in SAPS patients.[38,39] Dyslipidaemia was observed in 11.7% (2/17) of our patients which has also been reported in another APS cohort.[40] Among the obstetric manifestations of APS, preeclampsia has been observed as a common feature[5] and in our study cohort 7.1% (1/14) of the subjects showed preeclampsia. Sepsis was seen in 5.8% (1/17) of our cohort, presence of which is considered as one of the major causes of death in APS patients.[5] Among the neurological manifestations, only one patient exhibited epilepsy (1/17; 5.9%) although it is one of the most common non-criteria neurological manifestations in patients with APS.[41]

Laboratory features of the APS patients

LA was positive in 94.1% of the APS patients which is similar with Italian retrospective cohort of APS patients (12/13; 92.3%)[42] and higher than retrospective studies conducted in Hungary (170/637; 26.7%)[28] and Singapore (16/59; 27.1%).[13] aCL was positive in 81.8% of our cohort similar with the results of Euro-phospholipid project consisting of the APS patients of 13 European countries (817/1,000; 81.7%).[21] In line with our study, APS subjects of Euro-Phospholipid project also demonstrated higher frequency of ANA and anti-dsDNA presence in SAPS compared to PAPS patients ($p < 0.001$).[21] Mean PLT value of 29.4% (5/17) of our APS patients was lower than 100 x 10^9/L similar with the observation of APS patients of the Euro-Phospholipid project (296/1,000; 29.6%).[4] In terms of C4 levels, similar with our study, an European multicentre prospective study also observed lower levels of C4 in SAPS compared to PAPS subjects.[25]

Treatment strategies

Low intensity warfarin (INR target 2.0 - 3.0) was successful in our patient cohort (Table 2) in preventing recurrence of thrombosis which was also observed in a previous clinical study on APS.[43,44] Additionally, in our cohort, none of the combined treatment strategies (anticoagulant-antiplatelet and antiplatelet-immunosuppressive drugs) were successful in maintaining the targeted INR levels or thrombotic management. This might be explained by the possible drug interactions affecting the efficacy of anticoagulants.[37,45,46]

Limitations

(1) Only 17 APS patients from a single centre were reported. (2) Anti-β2GPI antibody was not evaluated in any of the APS patients of our cohort despite this being one of the three characteristic serum antibodies of APS according to the updated 2006 Sydney criteria,[1] and six of the APS patients were diagnosed after publication of the 2006 Sydney criteria. Nonetheless, majority of the APS patients exhibited LA (16/17; 94.1%) and aCL (9/11; 81.8%) positivity, concordant with studies on other APS cohorts from Southeast Asia where LA and aCL were positive in vast majority of APS patients.[11,47]

Conclusion

From this single centre 15-year retrospective study, high occurrence of pregnancy morbidity was observed compared to other cohort of APS patients. Other clinical features were also observed including menorrhagia, thrombocytopenia, ovarian cyst, lupus nephritis, dyslipidaemia, preeclampsia, sepsis and epilepsy. As both menorrhagia and ovarian cysts were observed remarkably in our cohort of APS patients, APS women of child-bearing age on anticoagulants should be monitored for the potential development of menorrhagia or rupture of ovarian cysts. As a successful treatment strategy, low intensity warfarin alone was successful in preventing recurrence of thrombosis compared to combined therapies. Future multicentre retrospective studies involving larger number of cases are recommended to elucidate the clinical, laboratory features and management strategies of Malaysian APS patients.

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