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Case Report Open Access

Severe Thromboembolism and Systemic Lupus Erythematosus Developing after Ovarian Hyperstimulation in a Persistent Carrier of Antiphospholipid Antibodies

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Abstract

Ovarian hyperstimulation (OH) is not a contraindication in selected women with antiphospholipid syndrome and/or systemic lupus erythematosus (SLE). A young woman who was persistently positive antiphospholipid antibodies, low protein free S and homozygous for the paraoxonase G192A mutation underwent three courses of OH; after the fourth course she developed severe thromboembolism and clinical features of SLE despite the use of a gonadotropin-releasing hormone agonist alongside aspirin that should have minimised the risk of OH syndrome. We provide a pathogenetic interpretation of these events in the light of the patient's investigations.

Keywords: Ovarian hyperstimulation; Antiphospholipid antibodies; Systemic lupus erythematosus

Background

Primary antiphospholipid syndrome (PAPS) is characterised by arterial and or venous thrombosis in the presence and persistence of antiphospholipid antibodies (aPL) in patients without any underlying autoimmune disorder [1]. A large series demonstrated that 23% of 165 PAPS patients progressed towards a well-defined systemic autoimmune disease during a mean 9.7 years of follow-up in the absence of any precipitating factors [2]. Ovarian hyperstimulation (OH) for ovulation induction does not represent a major concern in selected women with APS and/or systemic lupus erythematosus (SLE) provided patients prone to potential serious complications are excluded by a preliminary risk assessment [3]. A young who was persistently positive for aPL developed SLE and severe vascular events after OH allowing us to discuss some pathogenetic aspects inherent to her case.

Case presentation

In February 1996 a 22 year-old girl presented to neurology for right hemichorea of three days duration: a prolonged activated partial thromboplastin time (aPTT) was confirmed later as a lupus anticoagulant (LA). Her baseline and follow-up investigations are shown in Table 1. She had elevated IgG anticardiolipin antibody (aCL), strong LA, positive antinuclear antibody (ANA) (1:320), normal liver and kidney function tests, but no signs or symptoms of any autoimmune systemic disorder. Her free protein S was low (52%), much lower than the average of our other PAPS patients with acquired free protein S deficiency (84 ± 5.2%) [4]; we could not rule out hereditary free protein S deficiency as she had been adopted and did not know her parents. Amongst others she was also homozygous mutated for the paraoxonase (PON) G192A transition with a PON activity of 126 U/L compared to an average of 292 ± 86 U/L from 20 normal subjects.

A cerebral MRI revealed pin like lesions in the white matter of the basal ganglia bilaterally. Her hemichorea settled spontaneously but represented 12 months later only to disappear after 1 week of treatment with oral prednisone. A repeat cerebral MRI was unchanged compared to the previous one. She was started aspirin 100 mg daily. Two years later she married the son of her adoptive parents, but did she not conceive for almost 6 years during which concerns about fertility were raised. Her karyotype, infertility and hormonal tests, infection screen, assessment of tubal damage and of uterine abnormalities were normal. Her partner also had a normal karyotype but a degree of sperm hypomotility. As she moved to a different town, she was seen only once from February 2004: on that occasion and as part of the annual review of PAPS patients she underwent a doppler ultrasound of the carotid arteries and an echocardiogram: the former was normal but the latter showed a bicuspid aortic valve. From August 1997 to May 2000 she underwent three 7 day courses of ovulation hyper-stimulation with Gn-RH agonist combined with a Gn-RH antagonist, all covered by aspirin 100 mg that were uneventful but not followed by conception.

Two weeks after the fourth OH in 2005, she was admitted as an emergency for marked tachypnea, chest pain, jaundice, rash, ankle oedema, and joint pains. Investigations revealed Hb 7.6 g/dl, increased indirect bilirubin and LDH, positive direct antiglobulin test and undetectable haptoglobins in keeping with autoimmune haemolytic anaemia, platelets were $73x10^9$/L, albumin was decreased at 22 g/l, creatinine was raised at 255 mmol/L; there was proteinuria (2.8 g/24 hours) with slight haematuria. ANA and anti-ds-DNA were positive while C3 and C4 were low.

	Feb	Sept	Sep-97	Oct	Sept	May	Sept	Apr	Feb	Feb	
	1996	1996		1998	1999	2000	2001	2002	2004	2005	
KCTr	2.09	3.79	4	4.9	2.25	3.95	3.21	4.04	3.86	7.36	>1.30
aPTTr	2.37	4.05	3.89	3.41	4.06	3.46	4.05	3.8	3.48	3.24	>1.20
DRVVTr	1.46	1.9	1.97	2.11	2.13	2.16	2.33	2.18	2.09	2.76	>1.18
IgG aCL (GPL)	124	113	326	529	363	502	410	241	294	489	<20
IgM aCL (MPL)	12	23	25	46	16	31	32	50	14	89	<20
IgG β2GPI (IU/ml)							367		344		<12
FNG (mg/dl)	240	345	335		390	362	481	510	362	480	200-380
PS free (%)	52	49									
PS total (%)	90	80									
PC (%)	118										
vWF (IU/ml)	103	97	100		98		94				
PAI (mg/dl)	42	36					72				
HC (µmol/L)	16.9	12.6			12		18	10	14	13	<11.9
ANA	1:320			1:320						1:640	
Anti ds DNA	64			86						128	
C3 (mg/dl)	102			112						48	76-136
C4 (mg/dl)	89			98						46	14-76
			OH	OH		OH				OH	
			ASA	ASA		ASA				ASA	

Table 1: Base line and Follow up Investigations KCT: Kaolin Clotting Time; aPTT: Activated Partial Thromboplastin Time; DRVVT: Dilute Russel Viper Venom Time; r: Ratio; aCL: Anti Cardiolipin; ß2GPI: Beta-2-Glycoprotein-I; FNG: Fibrinogen; PS: protein S; PC: protein C; vWF: von Willebrand factor; PAI: plasminogen activator Inhibitor; HC: Homocysteine; ANA: Antinuclear Antibodies; OH: Ovarian Hyperstimulation; ASA: Acetylsalicylic Acid.

An abdominal and pelvic CT scan revealed bilateral pleural effusions and a left renal infarction, whereas a CT pulmonary angiogram revealed bilateral emboli; a transthoracic echocardiogram revealed severe aortic regurgitation that required an urgent replacement. She received high dose steroids, 6 pulses of cyclophoshamide 500 mg every three days followed by maintenance azathioprine, low molecular weight heparin in treatment dose (enoxaparin 120 mg s/c daily for 7 days) embricated with warfarin at a target INR range 2.0-3.0. After these events the patient moved out of the region but underwent an occasional review in April 2008: at that time she was still on warfarin and on azathioprine, her haemolytic anaemia had settled and the proteinuria ranged between 0.8-1.2 g/24 hours.

Discussion

The major risk of ovarian induction is OH syndrome that encompasses ovarian oedema, electrolyte imbalance, and diffuse capillary leak with resulting pleural effusions and ascites, and, at times, hypotension, hypercoagulability and thrombosis [5]. Vascular occlusions following OH have not been described in PAPS [6], but for a case of cerebral infarction developed in a PAPS patient with an obstetric history [7]; on the other hand intra-cardiac occlusion [8], ischaemic strokes [9,10] and catastrophic APS [11] have been described in carriers of aPL who had never suffered thrombosis. With regards to the development of SLE after PAPS, this has been detailed in two reviews over the last 12 years but OH was not involved in any of the progressions from PAPS towards SLE [12,13].

The thrombogenic potential of OH is unclear in isolated carriers of aPL and in PAPS patients: one possibility is a further increase in aPL titre after OH. Upon treatment with oestrogens, gonadectomized or intact male and female non-autoimmune C57BL/6 mice generate aPL that may persist for months after the oestrogen exposure [14,15]. In addition, an end-metabolite of 17-β-estradiol may induce the conversion B lymphocytes into immunoglobulin secreting plasma cells [16]. This would be in keeping with the finding of increased aPL titres in women receiving more than one course of OH for in vitro fertilization as well as explaining the aPL increase in our patient after

OH [17]. The latter study also showed that the elevated PL titre was negatively related to the antioxidant capacity of PON [17]. PON accounts for most of the antioxidant of properties of HDL against LDL oxidation [18] and its activity is known to be decreased in PAPS [19].

Interestingly, pregnancy negative infertile woman who never conceived had lower PON activity than women who became pregnant but OH increased PON activity promoting a favorable environment for implantation [20]. Our patient exhibited a 57% reduction of PON activity partly due to her homozygous PON G192A mutation and partly to her aPL favoring infertility and her PON activity could not rise after OH because of the same reasons.

It is well established that aPL are associated with an enhanced oxidative state [21] and any decrease of antioxidant capacity may favour oxidative stress that may further enhance thrombin generation with consequent vascular occlusions [22]. The need for thromboprophylaxis before OH had been stressed [23] but in our case aspirin cover proved insufficient and with hindsight enoxaparin should have been considered.

Conclusion

We have reported upon a persistent carrier of aPL who developed extensive vascular disease and SLE after OH despite aspirin cover. OH developed after the GnRH agonist/antagonist regime that should minimize the risk of OH syndrome at the expense of a lower 6% delivery rate compared to human chorionic gonadotropin [24]. The distinction between OH syndrome and APS remains semantic as thrombosis is a clinical feature of both, but a review of possible thrombogenic pathways should have led to maximising thromboprophylaxis with low molecular weight heparin for three months as suggested by the American College of Chest Physicians after resolution of clinical OHS syndrome (Grade-2C recommendation) [25]. Although we do our best as physicians to help unfertile women to conceive and carry on with their pregnancy, careful risk assessment should be applied in cases like ours to avoid disastrous outcomes after OH.

Consent

Written informed consent was obtained from the patient for publication of this Case report and a copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare no competing interests

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