CASE REPORT

The challenges of antiphospholipid syndrome: experience from diagnosis to self-care

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SUMMARY

A young woman presented to our unit with pancreatitis and acute kidney injury (AKI) 4 weeks after initiation of an oral contraceptive. She subsequently developed seizures due to posterior reversible encephalopathy syndrome and required ongoing haemodialysis for oliguric AKI. Routine antiphospholipid antibody screen was normal, but arterial and venous thromboses were identified on renal biopsy. Further coagulation studies identified an antiphospholipid-dependent inhibitor confirming the suspected diagnosis of antiphospholipid syndrome. She remained seizure free with control of hypertension and was established on anticoagulation. She remained haemodialysis dependent performing this independently at a new self-care unit. She provides us with valuable insights into her experience encouraging us to reconsider our current methods of education and communication in our younger population of patients living with chronic disease.

BACKGROUND

The various manifestations of antiphospholipid syndrome (APS) are well documented.¹ However, diagnosis can prove challenging due to the vast array of clinical presentations and various criteria for classification. This case describes a presentation of APS with confirmed arterial and venous thromboses, but normal lupus anticoagulant, anticardiolipin and anti-β₂-glycoprotein 1 antibody testing in a young patient. Communication with and management of adolescent patients can prove difficult for adult physicians; our patient's narrative, from admission to discharge and beyond, exposed shortcomings in our communication with her. Her feedback compels us to seek how we can individualise and optimise our care for adolescent patients.

CASE PRESENTATION

A 19-year-old female student was admitted with a 48 h history of severe abdominal pain, vomiting and anuria. She had been started on Yasmin contraceptive approximately 4–6 weeks prior to presentation. She had a medical history of gallstone pancreatitis requiring intensive care unit (ICU) admission, and subsequent cholecystectomy 3 years prior. Her family history was unremarkable.

On admission she had acute kidney injury (AKI), creatinine 478 μmol/L, with a metabolic acidosis and was transferred to ICU for haemodialysis. Blood pressure (BP) was 140/90 mm Hg. Initial CT of her abdomen was inconclusive for pancreatitis but repeat scanning a week later showed evolving pancreatic pseudocysts and swollen oedematous

kidneys (figure 1A, B). The AKI was felt to be secondary to acute tubular necrosis as a result of pancreatitis. Autoimmune and vasculitic antibody profiles, serum-free light chain ratio and immunoglobulin fractions were normal. No lupus anticoagulant was detected and IgG anticardiolipin antibody titres (3.1 GPLU/mL (range 0–20)) and anti-β₂-glycoprotein 1 antibody titres (3.3 U/mL (range 0–20)) were all within normal range. IgM levels of these antibodies were undetectable. Following return to the ward she reported headache, developed status epilepticus and was readmitted to ICU for seizure control. She was given empirical antiviral treatment for presumed encephalitis and received loading-dose phenytoin. CT of the brain, CT angiogram and lumbar puncture were normal and a diagnosis of posterior reversible encephalopathy syndrome (PRES) was entertained. High signal on T2-weighted imaging throughout the cerebellum, parietal and frontal lobes on an MRI of the brain were compatible with PRES (figure 2A, B). Maximum BP at this time was 150/100 mm Hg. She subsequently developed enterococcal sepsis treated with intravenous tazocin and vancomycin. She returned to the ward for further management. Following an afternoon of home

Figure 1 CT of the abdomen visualising a pancreatic pseudocyst (A, green arrow) and oedematous kidneys (B).

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Figure 2 MRI of the brain demonstrating increased signal on T2-weighted imaging in frontal lobes (A) and cerebellum (B).

leave she was readmitted having had a further seizure. Throughout admission she was anaemic requiring multiple blood transfusions and she had a positive Coombs' test. Platelet counts at this stage fell steadily over the next 14 days from 578 to $151 \times 10^9/L$, although there was no evidence from her blood film or other biochemical parameters to suggest haemolysis. She underwent a renal biopsy and had further acute abdominal pain afterwards. CT of the abdomen excluded retroperitoneal haemorrhage, and peripancreatic changes similar to the previous studies were noted. The renal biopsy demonstrated infarctive changes with venous and arterial thrombosis (figure 3). APS was now considered the most likely diagnosis and warfarin was started. Further coagulation studies were undertaken and the presence of an antiphospholipid-dependent inhibitor was detected. The use of a sensitive phospholipid reagent gave a prolongation in the activated partial thromboplastin time which did not correct further to the addition of normal plasma. The revised Sapporo criteria discussed by Miyakis *et al*² for a diagnosis of definite APS includes one clinical criterion drawn from (1) evidence of vascular thrombosis and, (2) pregnancy morbidity, including fetal loss, pre-eclampsia or three or more consecutive abortions in the absence of definite alternative causes. One laboratory criterion,

Figure 3 Renal biopsy specimen showing extensive necrosis.

namely positive lupus anticoagulant, medium or high anticardiolipin, or anti- β_2 -glycoprotein 1 antibody titres, is also required. Our patient did not have either detectable lupus anticoagulant or elevated titres of these antibodies. Miyakis *et al* discuss the use of other antibodies associated with APS which are not in themselves specific enough to include in the revised criteria. We suggest our patient had a non-criteria laboratory feature of APS; in order to establish whether the phospholipid-dependent inhibitor antibody in our patient was pathogenic, and neither transient nor a false positive, she would require repeat blood testing off warfarin therapy. Given the severity of the thrombotic episodes, stopping warfarin was felt to pose a significant thrombotic risk. It was therefore decided that stopping warfarin to test for persistent positivity of this antibody was unwise.

DIFFERENTIAL DIAGNOSIS

Initially acute tubular necrosis in the setting of pancreatitis was felt to be the cause of this patient's AKI, but this did not explain the seizures and lack of recovery of renal function. APS or thromboembolic disease was considered early given her new onset of seizures while mildly hypertensive, but initial routine screening antibody testing was negative. Normal vasculitic and antinuclear antibody profiles did not support a systemic vasculitis or systemic lupus erythematosus (SLE). Presence of a thrombotic microangiopathy such as thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome was doubtful in the absence of demonstrable haemolysis. IgG4-related disease, a cause of autoimmune pancreatitis and interstitial nephritis, was excluded by her normal serum levels and lack of IgG4 seen on retrospective staining of the previous cholecystectomy tissue. Paroxysmal nocturnal haemoglobinuria was excluded by normal flow cytometry analysis. Despite the updated APS criteria² the diagnosis in this case was challenging due to the normal titres of the antibodies. Demonstrable positivity of any one of these would have enabled a definite diagnosis of APS to be made. Ultimately the arterial and venous thromboses seen on renal biopsy enabled a unifying diagnosis of APS to be made with some confidence.

OUTCOME AND FOLLOW-UP

This patient remained haemodialysis dependent and has switched her care from the hospital unit to a self-care unit where she is independent in performing her dialysis. Follow-up MRI of the brain showed resolution of the previously identified parenchymal changes and excluded cerebral infarction as a cause of her seizures. She has remained seizure free and off anti-epileptic medication. Her parents have offered to be kidney

donors and are undergoing assessment for living-related kidney transplantation.

DISCUSSION

A wide variety of renal manifestations of APS have been described with thrombosis of renal vasculature possible at any level.³ Renal artery stenosis, renal infarction, renal vein thrombosis, microangiopathy and APS nephropathy have all been described associated with antiphospholipid antibodies (aPL).^{3,4} Various non-thrombotic renal conditions are also associated with APS such as membranous nephropathy, minimal change disease/focal segmental glomerulosclerosis, mesangial C3 nephropathy and pauci-immune crescentic glomerulonephritis.⁵ The prevalence of renal disease with primary APS is thought to be around 8–10% but this is likely an underestimate as these patients rarely undergo kidney biopsy because of thrombocytopaenia and/or anticoagulant treatment.⁴ Fortunately kidney biopsy in our patient allowed a diagnosis to be established in the setting of normal lupus anticoagulant and anticardiolipin antibody testing. Few patients develop end-stage renal disease with APS³ and renal prognosis is considered to be good. In studies which did find end-stage renal disease as a complication of primary APS, microangiopathic haemolytic anaemia was the commonest histological finding and SLE was thought to contribute in one case.^{6,7}

A wide range of abdominal manifestations of APS have been described, predominately affecting the liver but also the intestines, spleen and pancreas.⁸ A number of cases of acute pancreatitis associated with aPL and APS have been reported with initial autopsy reports suggesting possible thrombotic aetiology.⁸ Of note, CT of the abdomen performed on this patient 3 years earlier, at the time of presumed gallstone pancreatitis, identified a non-enhancing area in the pancreas suggestive of infarction. No gallstones were identified but she proceeded to cholecystectomy 3 months later. She had ongoing issues with abdominal pain and abnormal liver function tests following cholecystectomy, but a normal MR cholangiopancreatogram. It is possible that these episodes of abdominal pain were a result of minor recurrent thrombotic abdominal events prior to the presentation at our unit. A report by Spencer⁹ describes the case of a young female who presented with recurrent pancreatitis and who subsequently developed seizures as a result of cortical vein thrombosis. Anticardiolipin antibodies were positive and she was diagnosed with primary APS.⁹ It was concluded that the investigation of patients with idiopathic pancreatitis should include checking aPL. A further report by Nguyen *et al*¹⁰ describes a case of APS in a 38-year-old woman presenting with a hypertensive emergency, AKI and necrotising pancreatitis.

Patients with APS commonly suffer from cerebrovascular disease but other neuropsychiatric features have also been described including epilepsy, headache, transverse myelitis, chorea, idiopathic intracranial hypertension, multiple sclerosis, dementia and depression.¹¹ PRES is recognised in the setting of a number of conditions including hypertensive encephalopathy or acute rise in BP, eclampsia, autoimmune disease and ciclosporin toxicity.^{12,13} A further case report has also described PRES in the setting of APS.¹³ Possible mechanisms include transient ischaemia or a direct effect of the aPL causing increased vascular permeability or activation of vasoactive substances.¹⁴ An acute sustained rise in the diastolic BP (>100 mm Hg) is a risk factor for PRES.¹⁴ The authors of this case report felt that APS may put the patient at an increased risk for developing PRES with only a minor rise in BP, a finding recognised in other

cases.¹⁵ Our patient required three antihypertensive medications to ensure rigorous BP control.

Combined oral contraceptive (OC) use is a recognised risk factor for thrombosis due to its oestrogen content. Other cases of APS have been identified following a thrombosis while taking OCs.¹⁶ There is little evidence to inform the duration of anticoagulation in those with APS and a single episode of thrombosis triggered by a transient secondary risk factor (OC use, pregnancy, hormone replacement therapy or surgery).¹⁷ Owing to the devastating nature of our patient's thrombotic events,

Patient's perspective

Communication

- On discussion with the patient 10 months following discharge, she felt that she had good knowledge of her condition; however, during her admission her understanding was limited. She commented that she was perhaps 'too sick to understand' or that maybe she did not want to hear. She was aware that she was in the intensive care unit but did not know why she was getting continuous renal replacement therapy in the form of venovenous haemofiltration as it was not explained to her. An abiding and unpleasant memory was that it always made her feel very cold.
- The repeated interrogations at time of admission regarding whether she had taken any illicit drugs annoyed her, and she felt that she was not being believed by the nurses or doctors. She recalled patronising comments from staff at times, such as being scolded for dietary indiscretions of which she was unaware and for not providing her 'yellow book' for warfarin dosing. This added to the sense of guilt that she had done something wrong and that all of this was her fault.
- She felt that the majority of communication regarding her condition was directed to her mother who then discussed with her. At times staff gave mixed messages. Examples included conflicting plans for renal biopsy, and a meal with peas arrived at the same time a dietician counselled about not eating peas. The 'watershed' moment for her was being told that her dialysis line was going to be changed to a permanent catheter. This information was imparted to her in a matter of fact way with no time given to process or respond to it. She would have preferred to have had more guidance at that time and perhaps to have seen another patient with a tunnelled line. Other patients on her ward had issues with their lines, and she was concerned that this would affect her also. She appreciated time taken by younger consultants for one-to-one discussion with her. However, her overall impression was that during hospital admission, counselling and education was generally rushed. Even at the time of discharge she still was not fully aware of what 'having no kidneys' would entail.
- Following discharge she did not find the renal education programme (DVDs and seminars) appealing and found that nurses at the haemodialysis unit were too busy for lengthy discussions. Nobody had told her that a renal transplant would not last forever so the early exposure to patients in the dialysis unit with failed transplants was a shock. The home therapies nurse, who trained her to do self-care haemodialysis, provided the best education for her and she valued the time taken to answer her questions.

Psychosocial impact

- ▶ Haemodialysis is the centre of her life and she regards it as a 'full-time job.' She finds the routine physically and mentally exhausting and resents the loss of spontaneity in her lifestyle. Unfortunately she has not yet been able to return to studying despite her place of study being very supportive. Following the transfer of her care to the new self-care unit, she feels much better physically and is able to go out more to meet up with friends. Regaining her driving licence following her seizures was very important for her independence. She finds her dialysis line cumbersome and it frustrates her that she cannot go swimming due to the risk of infection. Regarding her diet, she reflects that "phosphate is the bane of my existence" as she frequently forgets to take binders with her meals.
- ▶ This patient gains most support from another male patient at the self-care unit who is of a similar age. She enjoys talking to him as she states she has little in common with the majority of elderly patients in the hospital unit. At one time an elderly patient in the parent dialysis unit asked, "are you lost, love?", failing to recognise her as a fellow patient. There was limited chance for social interactions in the hospital unit as the nurses were generally busy during the evening dialysis shift, and patients had their own TVs to watch.
- ▶ Humour is a helpful coping mechanism for her. Frequently she asks friends and relatives what blood type they are, 'screening them' for potential transplant donors. She is focused on renal transplantation and the potential for return to 'normality'. Her father and mother (who is a nurse) are very proactive regarding her condition. Her brother was reluctant to be tested for suitability as a possible donor match but she reports this has not impacted the relationship between them.

lifelong anticoagulation has been recommended and she has been advised to avoid future oestrogen therapy. She will require warfarin reversal and plasma exchange when she undergoes a living-donor renal transplant.

On discussion with the patient, she raised various issues with our communication and education methods during her time in hospital and as an outpatient. This is detailed in the patient experience section above. Management of adolescent renal patients can prove challenging, whether they are in transition from paediatric nephrology or newly starting on renal replacement therapy like this patient.¹⁸ Our education programmes are often targeted towards elderly comorbid patients with progressive chronic kidney disease. Presenting at the age of 19 years with a life-threatening illness that then leads to end-stage renal disease and the need for lifelong renal replacement therapy is devastating. Education methods must be tailored to the individual, and it is critical to their ongoing management that the patient learns to trust the healthcare team. Physicians should ensure that time is set aside to allow for one-to-one discussions with individuals and to ensure adequate understanding; for adolescents, it is important that the healthcare team communicate directly to them rather than via their parents. Poor communication frequently led to our patient misunderstanding vital information and this negatively impacted her experience. We need to recognise when 'watershed' moments come for patients who

may be entering for the first time a chronic disease pathway; these moments may simply be the initiation of new medication. For this patient, it was the insertion of a permanent haemodialysis catheter. Medical and nursing staff should take time to ensure that patients have time to process thoughts and feelings, are given ample opportunity to ask questions and that understanding is achieved before discharge.

Learning points

- ▶ Establishing a diagnosis of antiphospholipid syndrome (APS) may be complicated by the wide variation of disease manifestations, extensive criteria for classification and limited potential for renal biopsy due to coagulopathy.
- ▶ A 'normal' routine antiphospholipid screen may not exclude a diagnosis of APS so clinicians should maintain a high level of suspicion and ensure early collaboration with their haematology colleagues.
- ▶ Communication and education should be individually tailored for all patients but especially for young adults. Consideration of the physical, psychological and social impacts of the diagnosis of end-stage renal disease in this age group is vital to ensure optimal patient-centred care.

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