Alendronic acid 70 mg, calcium and vitamin D supplements. Patient had severe vitamin D deficiency and was commenced on treatment at primary care. She is on analgesics and physiotherapy for back pain, which was of moderate severity. She was on oral prednisolone for 5 years for polymyositis rheumatica in the past and weaned off year ago. Other past medical history includes coronary artery disease; a myocardial infarction requiring coronary artery bypass graft 3 years back. She does not have diabetes or hypertension. She has hypercholesterolaemia; probably polygenic in origin and is on lipid lowering medications since the age of 50 years.

Her alcohol intake is minimal, and is a non-smoker. There is no family history of osteoporosis or cardiovascular disease. Her milk consumption accounted for 300 mg of calcium per day. She has reached menopause at 43 years of age and has not been on hormonal replacement therapy. Her current medications are Aspirin, Atorvastatin, Bisoprolol and Omeprazole. There is no history of indigestion or dental concerns.

Except mild local tenderness at L4–5 region, rest of the clinical examination is unremarkable.

Recent blood investigations showed normal calcium, inorganic phosphate, PTH and vitamin D. Alkaline phosphatase (195 IU/L) and P1NP (55 ug/L) were raised. Renal functions showed normal creatinine with eGFR of 62 mL/min. Full blood count is unremarkable. Serum and urine electrophoresis excluded multiple myeloma.

Summary: This is a case of severe osteoporosis involving vertebral fractures requiring osteoporosis treatment. Possible causes for osteoporosis would be previous use of oral steroids for long time and severe undiagnosed vitamin D deficiency. Hypercholesterolaemia and significant history of ischaemic heart disease are other concomitant diagnoses.

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Emerging topics in the management of the antiphospholipid syndrome

SP0164 HOW TO MANAGE ASYMPTOMATIC CARRIERS OF ANTIPHOSPHOLIPID ANTIBODIES

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Individuals who do not display the classical features of the Antiphospholipid Syndrome (APS) (vascular and obstetric disease)¹ are referred to as “aPL carriers”. They can be patients affected by systemic autoimmune diseases who are screened for antiphospholipid antibodies (aPL). aPL may be found in patients with “non-criteria” manifestations or in women undergoing investigations for infertility. The presence of aPL can be serendipitously discovered before a surgical procedure because of a prolonged thromboplastin time. Are these subjects at increased risk for thrombosis and adverse pregnancy outcomes (APO)? Since aPL are pathogenic autoantibodies, the answer should be “yes”. However, the magnitude of the risk can be variable from patient to patient, accordingly to the multifactorial origin of aPL-related vascular and obstetric manifestations.

According to international consensus,² the thrombosis risk stratification should consider: 1) the aPL profile (type, titer, persistence), 2) the coexistence of other thrombotic risk factors, and 3) the presence of an underlying autoimmune disease, mainly systemic lupus erythematosus (SLE). The definition of “high-risk” aPL profile comprises positivity for Lupus Anticoagulant (LA), or ‘triple positivity’, i.e. LA+anti cardiolipin antibodies (aCL) +anti-beta2glycoprotein I antibodies (anti-B2GPI) or medium-high titers of IgG aCL or IgG anti-B2GPI. Conversely, patients with isolated, intermittently positive aCL or anti-B2GPI at low-medium titers could be considered at low risk for thrombosis.

According to the literature, aPL carriers seem to have a low annual incidence of acute thrombosis, ranging from 0% to 3.8%³. These figures are not much different from the estimated incidence of thrombosis in unselected cases (about 1% patient-years), which is also equivalent to that of major bleeding associated with the use of low dose aspirin (LDA), the most frequently used drug for primary prophylaxis.⁴ Therefore, the dilemma in clinical practice is to correctly select those aPL carriers for whom the expected benefit of therapy outweigh the risk.

Over years, the management of aPL carriers have been investigated in several studies enrolling different patients groups (SLE, pure obstetric APS, asymptomatic aPL carriers) and evaluating the efficacy of various interventions: LDA,⁵ low intensity warfarin,⁷ low molecular weight heparin (LMWH) in high risk situations such as surgery, prolonged immobilisation, and puerperium.⁹

Aside from drugs acting on platelets and on the coagulation system, there is evidence that immunomodulatory agents may be beneficial in primary prophylaxis of aPL carriers. Hydroxychloroquine (HCQ) is a well-recognised key-drug in the management of SLE patients and has an anti-thrombotic effect.¹⁰ The use of HCQ as primary prophylaxis has been proposed also for non-SLE patients.¹¹ Statins may be useful in aPL carriers not only for the correction of a proatherogenic lipid profile, but also for reducing proinflammatory and prothrombotic biomarkers.^{12,13}

Turning to the obstetric field, the detection of aPL antibodies has been increasingly performed in asymptomatic women, mainly for obstetrical reasons (e.g. before assisted reproductive techniques, after APO that are not included in APS classification criteria). Therefore, it is not infrequent to take the responsibility to recommend or not a treatment in “healthy” pregnant women carrying aPL. General obstetric risk should be assessed (age, hypertension, obesity, etc.). It is currently under discussion whether different aPL profiles confer the same degree of obstetric risk.¹⁴ LA¹⁵ and triple aPL positivity¹⁶ seem to be the major predictors of APO, although APO have been described also in patients with a “low-risk” aPL profile (e.g., IgM isotype or medium to low aPL titers).^{17,18} A key drug for primary obstetric prophylaxis is LDA and many physicians prescribe it to pregnant aPL carriers.²⁰ The immunomodulatory properties of HCQ have been advocated to be beneficial in pregnant patients with aPL²¹ and clinical retrospective studies supported its effectiveness in refractory obstetric APS.^{22,23} Puerperium is considered a high-risk period for thrombosis for all women. Women who carry aPL should be considered for LMWH for 4–6 weeks after delivery.¹⁹

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SP0165 THE COMPLEX INTERPLAY BETWEEN SYSTEMIC LUPUS ERYTHEMATOSUS AND ANTIPHOSPHOLIPID SYNDROME

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The antiphospholipid syndrome (APS) was first described in the 1980's. It is diagnosed when antiphospholipid antibodies (aPL) i.e. anti-cardiolipin (aCL), anti-β₂Glycoprotein-I (aβ₂GPI) or positivity in the functional lupus anticoagulant test (LA) occur together with any type of thrombosis (e.g. myocardial infarction(MI), stroke, venous or microvascular thromboses) or obstetric complications.⁵ aPL recognise protein co-factors, most importantly the scavenger protein β₂GlycoproteinI (β₂GPI), that bind to membrane phospholipids. It is not fully understood how complexes of β₂GPI and anti-β₂GPI antibodies initiate a pro-thrombotic state, but activation of platelets, endothelial cells and the complement cascade are associated features.

Approximately 80% of APS patients are women, many are young and severely ill. There is a considerable overlap between APS and SLE. Approximately 30%–40% of SLE patients are aPL positive but only about half of them develop clinical symptoms fulfilling the APS classification criteria.

Several prospective studies have demonstrated that aPL are predictive of vascular events in patients with SLE. Though conflicting results exist, we have not noted positive associations between aPL and accelerated atherosclerosis in SLE, rather we believe that it is the pro-thrombotic state, which is the major cause of vascular events in the aPL positive SLE subgroup. Microvascular disease is an often unrecognised and difficult to diagnose feature in the aPL positive SLE subgroup. We have noted that up to 15% of patients diagnosed with nephritis have microvascular pathology in accordance with APS nephropathy in renal biopsies.

The aPL positive SLE subgroup has also been demonstrated to have a more rapid accrual of damage, where in addition to vascular damage neuropsychiatric damage makes a notable contribution.

When investigating primary APS patients, we and others have noted traits that are normally seen and attributed to SLE, such as low platelets, complement consumption, a low grade of systemic inflammation and even low titers of anti-DNA antibodies. Thus, the distinction between these two groups, APS secondary to SLE and primary APS, is not always clear.

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SP0166 ALL YOU NEED TO KNOW ABOUT KIDNEY DISEASE IN ANTIPHOSPHOLIPID SYNDROME

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Antiphospholipid syndrome (APS) can affect any vascular bed and is characterised by a plethora of clinical manifestations related with different organ systems involvement. Accordingly, APS can affect any part of kidney vasculature and parenchyma such as renal arteries and veins, intra-renal arteries and arterioles, and glomerular capillaries. APS-associated nephropathy was first described in patients with primary APS, characterised by acute thrombotic lesions in glomeruli and/or arterioles (thrombotic microangiopathy) and chronic vascular lesions such as fibrous intimal hyperplasia of arterioles and interlobular arteries, organised thrombi with or without recanalisation, and fibrous arterial and arteriolar occlusions or focal cortical atrophy.¹ APS nephropathy lesions have also been later described in patients with SLE-associated APS and SLE patients with positive antiphospholipid antibodies but without APS, independently of lupus nephritis.^{2, 3} The most common clinical manifestations of APS nephropathy include hypertension, microscopic hematuria, proteinuria (from mild to nephrotic range), and a usually mild renal insufficiency. Arterial thromboses (especially stroke), pulmonary embolism, livedo reticularis, anticardiolipin antibodies, and lupus anticoagulant were strongly associated with histologic lesions of APS nephropathy. During the follow-up period, manifestations of APS (especially arterial thromboses) developed more frequently in SLE/non-APS patients with APS nephropathy than in those without APS nephropathy lesions. In the Sydney classification criteria for APS, APS nephropathy has been included in non-criteria APS manifestations.⁴ The significant association between the presence of APS nephropathy and antiphospholipid antibodies suggests a pathogenetic role of antiphospholipid antibodies in the development of this nephropathy. Data from experimental and clinical studies support also a potential role of complement cascade activation, tissue factor activation, and activation of mTORC in APS nephropathy pathogenesis. Currently, there is no consensus on the treatment of APS nephropathy. Updated evidence about the role of anticoagulation, hydroxychloroquine, statins, and targeted therapies such as B-cell directed therapies, complement inhibition, tissue factor inhibition, and mTOR pathway inhibition will be discussed.

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The links between gout and kidney function

SP0167 RENAL URATE TRANSPORTERS (SUMMARY FOR CLINICIANS)

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Gout was, and still is in some academic environments, a “metabolic” disease. The advent of allopurinol in the mid of the XXth century, the first xanthine-oxidase inhibitor, precluded that most subjects with “primary gout” were to suffer from overproduction of uric acid. No actual overproduction was neatly demonstrated and some empiric observations showed that “renal underexcretion” was working in most patients with gout.

In 2002, Enomoto and coworkers characterised the first renal urate transporter, URAT1, encoded by SL22A12, showing that the human knockout for URAT1 was associated with familial hypouricemia. A bunch of uric acid transporters have been characterised since then, polymorphisms of some of them being associated with variability in renal handling of urate. The function of transporters is complex: PDZK1 (also known as NHERF3) is a scaffolding protein that binds to several urate transporters such as URAT1, OAT4, and NPT1. Therefore, PDZK1 plays a pivotal role in forming a urate-transporting multimolecular complex (also named “urate transportome”) in humans. Hyperuricemia is no more a metabolic disease: it is a “transportopathy”. In addition, linkage of urate transporters to Na, P, and sugars may help understanding some comorbid conditions associated to hyperuricemia and gout, such as diabetes and hypertension.

In addition to the previously referred, ABCG2 is a cassette binding protein expressed in the kidney and more importantly in the intestine, where is involved with active excretion. The discovery of ABCG2 helped to explain that apparent overproduction in some patients is a “renal overload” due to impaired intestinal excretion.

A summarised knowledge on the urate transporters may be useful for clinicians implicated in the management of gout, as it may explain why XOIs efficacy does differ in patients with apparent overproduction, why allopurinol response may be blunted in some patients, how targeting transporters may be helpful for the development of new urate-lowering molecules, and how to explain efficacy and safety models for uricosurics and combination therapies.

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SP0168 THE USE OF XO INHIBITORS IN CKD – PROS AND CONS

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The association of chronic kidney disease (CKD) and hyperuricaemia is well established, and many observational studies have reported that hyperuricaemia is associated with development and progression of CKD. Potential mechanisms of this observation will be discussed, including the potential for urate as an ‘innocent bystander’ or as a causal mediator contributing directly to kidney injury. Xanthine oxidase inhibitors (XOIs) are the most widely used urate-lowering drugs. Current evidence for efficacy and safety of XOIs for preventing or delaying progression of chronic kidney disease will be presented, both in the general population and in people with gout. The challenges of XOI use in people with CKD will also be discussed, with specific reference to allopurinol dosing in CKD, and cardiovascular safety of febuxostat.

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Big data in pre-clinical research

SP0169 INTEGRATION OF OMICS DATA FOR PREDICTING RESPONSE TO ANTI TNF TREATMENT

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Successful development of biologics for targeting specific molecules, like TNF, was a hallmark of new era in therapy of inflammatory and rheumatic diseases.