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Dear Sir,

Early diagnosis of inflammatory joint and connective tissue disease is key to achieving effective treatment and improved prognosis. Notably, it also impactsin a patient's quality of life. While the importance of early diagnosis in the management of mostrheumatic diseases is undisputable, it is still unrecognisedin patients with antiphospholipid syndrome(APS). This is important to address asthe prompt identification of antiphospholipid antibodies (aPL) regulatesthe strategy of treatment, impacting the management in both pregnancy-related and thrombotic-related events, with the ultimate aim of reducing the risk of recurrences and improving patient's prognosis and, thus, their quality of life. For rheumatoid arthritis, diagnostic delays are usually due to gaps between symptoms onset and the referral to a specialist. Inpatients with APS, in addition, a diagnostic delay might also occur dueof the heterogeneity of symptoms and the high prevalence of thrombosis and pregnancy complications in the general population(only a minority of which are attributable to APS). The identification ofaPLguidesthe management of these patients where indefinite anticoagulation will take the place of 3-6 months anticoagulation given in patients with non aPL-related venous thrombosis. Therefore, the diagnostic accuracy of aPL testing is crucial. Currentlaboratory classification criteria for APS include lupus anticoagulant(LA), anti-cardiolipin (aCL) and anti-β2GPI (anti-β2GPI) antibodies. While this panel of tests can correctly identify the great majority of the cases, some patients may be not identified despite overwhelming clinical suspicion of APS.

The diagnostic setbacks have been recently reviewed [1]. Herewith, we will share how the diagnostic challenges reflect in a patient's journey to reach the most effective management strategy.

A 49 years oldwoman, with a history ofsixunexplained early miscarriages in her 30s, developed a new onset of purpura at her low limbs. Inthe emergency room, her platelets levels were found as low as 4000/mm^3 and she was managed with high doses of steroids with gradually resolution of the thrombocytopenia. During the admission she was found to be negative for aCL and anti-β2GPI antibodies; LAresults came backlabelled as dubious and not repeated at the time. After 3 months, shepresented again to the ER with diffuse abdominal pains and hemiplegic lower limbs with delayed peripheral pulses. Angio-CT scan showed a massive abdominal aortic thrombosis. She successfully underwent emergency surgical aortic thrombectomy, she was stared on anticoagulation therapy and she gradually recovered. When her story was re-evaluated at our Center, LA testing results were still reported as equivocal,aCL and anti-β2GPI antibodies were negative, but she was found to be strongly positive for anti-phosphatidylserine/prothrombin antibodies (aPS/PT), a non-criteria aPL used within the research setting[2]. She is now stable on long-term aspirin and warfarin.

What have we learned from this patient's story? APS is a low-prevalence disease, and patients who suffer from rare diseases often encounter diagnostic difficulties that subjectssuffering from more common disorders are spared. Fewer health care providers have enoughknowledge and experience to handle a rare disease and usually none or much fewer therapeutic options are available. Moreover, this lack of awareness of the clinical manifestations of a rare disease may lead to a diagnostic delay, a failure of diagnosis, and even misdiagnosis[3,4].statistics showed that up to 25% of the patients with a rare disease waited more than 3 years before the correct diagnosis;about 40% wereinitially misdiagnosed, including 7% who weretold that their symptoms were psychological/psychiatric. Patients often must find answers on their own to obtain the

correct diagnosis. Besides, diagnostic delaysleadto loss of confidence in the health-care system in about 20% of the patients [REF – Savino questa non so dove trovarla].

In selected cases, given the appropriate clinical setting, aPL testing might go beyond the recommendations of availableclassification criteria. While itisimpossible to determine if the thrombotic event was somehow avoidable, one could speculate that an earlier identification of aPS/PT wouldhave confirmed the suspicion of APS with the immediate establishment of primary thrombo-prophylactic measures. Classification criteria are a set of characteristics that are used to group patients into well-defined homogenous populations that share similar clinical features of a disease.For autoimmune conditions, such criteria are often developed to select homogenous cohorts of patients for clinical research. Although the use of classification criteria as diagnostic is common in clinical practice, their suitability is debated as they do not usually recognise the wide spectrum of clinical manifestations. In fact, in the context of low-prevalence autoimmune conditions, classification criteria fail to encompass all aspects of a disease, including both clinical manifestations and laboratory-based findings.

Undoubtedly, a delay in diagnosis impacts on quality of life and prognosis. During the often quite extended interval between the appearance of the first manifestations of a rare disease and its correct diagnosis, patients live in a diagnostic vacuum if their symptoms remain medically unexplained and lack a follow-up plan. This situation, as Nettleton et al[5] demonstrated, is often described as "a merry-go-round of hope and despair". Such strong feelings suggest that a prolonged pre-diagnostic period is stressful and traumatic and may haveserious effectson the mental health of the patients involved, even possibly in the form of post-traumatic stress symptoms.

Since the first descriptionof the syndrome in 1983, the number of antibodies that have been associated to APS is constantly increasing. We are now facing the challenge of correctly attributing value tonew antibody specificities, such as aPS/PT and anti-Beta2GPI-domain 1, in the diagnostic algorithm of APS, with the final aim to improve diagnostic accuracy, leading to a better prognosis and quality of life.

Figure 1. Suggested diagnostic algorithm for APS and aPL screening.

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