Screening for Pulmonary Hypertension in Antiphospholipid Antibody Positive Lupus Erythematosus

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Pulmonary hypertension (PH) is a serious complication of systemic lupus erythematosus (SLE). This association was once considered to be rare. However, since 1981 several cases of SLE associated PH (SLEaPH) have been reported from different countries including India, suggesting that this complication is not uncommon. A systematic review of the literature up to 2012 revealed, 22 well documented studies including 642 cases in Chinese population. Analysis of these cases showed that SLEaPH typically affects middle-age women and is often characterised by non-specific symptoms and poor prognosis. Early identification and standard PH treatments as well as intensive SLE treatment can improve the prognosis of SLEaPH.

The classification of PH has gone through a series of changes since the first classification proposed in 1973 which designated only two categories, primary pulmonary hypertension and secondary pulmonary hypertension depending on the presence or absence of identifiable causes or risk factors. The terms primary and secondary pulmonary hypertensions are now obsolete. According to the latest classification of PH – now known as Dana Point Classification from the location of Fourth World Symposium on Pulmonary Hypertension 2008, PH is divided into five subgroups:

**Group 1: Pulmonary arterial hypertension (PAH).**

**Group 2: PH due to left heart diseases.**

**Group 3: PH due to respiratory diseases.**

**Group 4: Chronic thrombo-embolic PH.**

**Group 5: PH with unclear multifactoral mechanisms.**

The pathogenesis of PH in SLE can be multifactorial, but pulmonary arterial hypertension (PAH) is the commonest cause. This is characterised by increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest as assessed by right heart catheterisation and with normal pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg. Chronic thrombo-embolic state, interstitial lung disease, venocclusive disease and myocardial involvement can occur in minority of SLE patients. This suggests that all but group 5 of Dana Point classification can occur in SLEaPH.

Despite the increasing recognition of SLEaPH, diagnosis is often delayed. This may lead to unfavourable outcomes. Lian et al suggested that more than 40% of the SLEaPH patients have no symptoms in the early stage of PH. One of the reasons for this is that patients with connective tissue disease like SLE, may be relatively sedentary and therefore do not develop symptoms until their disease is quite advanced.

In general, the clinical symptoms of SLE patients with PH are nonspecific such as progressive exertional dyspnoea, chest pain, non-productive cough, oedema, easy fatigue, impaired exercise tolerance. These can be caused by many other factors including pleural or pericardial effusions, interstitial lung disease, making it possible to miss the diagnosis. Such patients may present to the internist for management and the treating physician should have a high index of suspicion for SLEaPH and screen the patients accordingly.

Screening is defined as the systematic testing of asymptomatic individuals for preclinical disease. The purpose of screening is to identify those with mild symptoms and to prevent or delay progression of disease through early management. Screening programmes play an important part in the detection of PH in certain “at-risk” populations and may enable patients with PH to be identified at an earlier stage than in routine clinical practice. In the study by Lian et al the predictors contributing to SLEaPH were identified. The leading predictors of SLEaPH were found to be Raynaud phenomenon, anti-U1 RNP antibody, anticardiolipin (aCL) antibody positivity and serositis.

Antiphospholipid antibodies

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(aPL) comprise a heterogeneous group of antibodies directed against phospholipids and or protein complexed phospholipids. aPL are associated with the serious autoimmune condition antiphospholipid (antibody) syndrome (APS). aPL are assayed within the laboratory using either ‘solid phase’ assays that indentify aCL antibodies and anti-ß2-glycoprotein I antibodies (aß2GPI) and liquid phase assays that identify lupus anticoagulants (LAs). Retrospective and prospective studies have shown that triple aPL positivity (i.e aCL, aß2GPI, plus LA) correlates more strongly with thrombosis than the presence of single or double positivity. aPL have been associated with two types of PH, the thromboembolic type after deep venous thrombosis in the lower limbs complicated by pulmonary embolism and the primary plexogenic type. Several studies have investigated whether presence of anti-phospholipid antibodies in SLE predicts the development of PH. In a study of 55 patients of SLE form North India, Kaolin clotting time was used to screen for LA which was detected in 13% of these patients. No statistically significant association was found between LA and PH possibly due to the small sample size. On the other hand a study carried out in UK, found a significant association of LA and presence of APS in SLE cases with PH. More recently a study from Turkey found more patients with SLEaPH had aCL antibodies but no difference was found in respect to LA. On the other hand, a study from Tunisia found 25% of lupus patients with PH has had positive antiß2GPI antibodies as opposed to 12% of lupus patients without PH. In the current issue of JAPI, Ware et al studied 50 patients of SLE and categorised them into two groups: aPL positive and aPL negative. All the three aPL assays were done in each patient (aCL, aß2GPI antibodies) and dRVVT (dilute Russell viper venom time and activated partial thromboplastin time- aPTT for LA). Both the groups were screened for PH for trans-thoracic echocardiogram and patients with moderately severe PH were screened for thromboembolic PH by CT pulmonary angiography and lower limb venous Doppler. Eleven aPL positive patients had SLEaPH and six out of these eleven had double or triple aPL positivity. No cases of thromboembolic PH were detected in this study. These findings are very similar to the findings in previous studies regarding relationship of SLEaPH with antiphospholipid antibodies. The study by Ware et al has main limitation that the study is observational and uncontrolled nature meaning that only inferences rather than firm conclusions can be made regarding the predictive role of aPL antibodies in SLEaPH. Pregnant patients were excluded from the study. This exclusion introduces a selection bias. PH presents a considerable management challenge especially when diagnosed during pregnancy as the condition can deteriorate rapidly. Screening of pregnant SLE cases for PH can help in early diagnosis of this condition and use of multidisciplinary approach can improve maternal prognosis and survival. The study was carried out at a tertiary care centre in Mumbai, implying “referral bias” About half the number of cases had moderately advanced PH. In a study carried out in UK, patients were from community-based lupus cohort and majority of cases had mild PH. Despite the obvious limitations, the study by Ware is a step forward confirming the potential role of aPL antibodies in SLEaPH. Further research on this topic is needed to answer the question whether triple aPL antibodies positivity is a better predictor of SLEaPH as compared to single or double aPL positivity.

References


