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Management of Systemic Lupus Erythematosus complicated with Refractory Immune Thrombocytopenic Purpura and Pulmonary Artery Hypertension

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Abstract

The coexistence of immune thrombocytopenia (ITP) and pulmonary artery hypertension (PAH) is rarely observed as the initial manifestation of systemic lupus erythematosus (SLE), often leading to delayed diagnosis and poor outcome. We presented the case of an 18-year-old female of Asian origin with severe ITP and PAH as the initial manifestation of SLE. The patient was successfully treated with a combination of methylprednisolone, mycophenolate mofetil, sildenafil, and vinca alkaloid (vincristine). This case provided the opportunity to increase awareness of an uncommon association between SLE complicated with ITP and PAH and suggest a positive impact of early diagnosis and appropriate treatment on the patient's outcome. The use of vincristine was considered as per the guideline on refractory ITP before referral for splenectomy.

Introduction

The systemic lupus erythematosus (SLE) is an autoimmune disease that affects both females and males of all ethnic groups at the ratio of 10: 1. However, the ratio is significantly lower (2:1) in children and the elderly [1]. SLE predominantly presents with hematological, renal, and central nervous system involvement due to immune impairment caused by complex deposition of autoantibodies [2]. Immune thrombocytopenic purpura (ITP) (defined as a peripheral blood platelet count <100 × 10 /L) is its major hematological complication. When ITP fails to respond to first-line therapy, it is known as refractory ITP [3].

ITP is believed to influence pulmonary arterial hypertension (PAH) in SLE, though anti-Ro(SS-A) / anti- La (SSB) antibodies are regarded as risk factors [4]. Although rarely reported, PAH is the 3rd leading cause of mortality in Chinese SLE patients. PAH is diagnosed by echocardiography (systolic pulmonary arterial pressure > 40mm Hg) and right heart catheterization criteria (mPAP ≥ 25 mm Hg, PAWP ≤ 15 mm Hg) [5]. Mortality rate due to SLE-PAH is 83.9% [4]. Annexing ITP to condition worsens morbidity and mortality rates, and management exceptionally challenging.

Case report

An 18-year-old female of Asian origin was diagnosed with SLE ten years ago based on a positive anti-dsDNA and positive anti-nuclear antibodies (ANAs). She experienced good health until four days before admission. She was admitted to our facility due to malar rash, dysphagia, generalized body weakness, malaise, and fatigue. A detailed neurologic examination showed no focal neurological deficits. She presented with a normal level of consciousness and vital signs. She had pallor, malar rash, local telangiectasia, bilateral muscle tenderness, and weakness of the lower limbs. Fingers of both hands presented with scaly violet-colored erythema on the extensor surface. Observation of the chest area revealed flaky dusky red erythema.

Laboratory exams revealed BUN 10.0 mmol/L, creatinine 102 umol/L, urea 564 umol/L, AST 40.5 U/L, and ALT 375.30 U/L. Prothrombin time normal ranges. ANA positive (1:640), anti-dsDNA positive (80 IU/mL), hypercomplementemia (C3 <43.6 mg/dL, C4 < 4.0 mg/dL), RF 22.4 IU/ml, ESR 59 mm/hr, hypergammaglobulinemia (IgM 2.79 g/L, IgG 27.98 g/L), Pancytopenia (WBC 2.71*10^9/L, Hb 89 g/L, platelets 23*10^9/L). Urinalysis with abundant erythrocytes and 5-10 leucocytes per high power field. 24-h urine protein showed 899 mg/24hrs. Echocardiogram revealed pulmonary hypertension (49 mmHg), with the normal function of cardiac chambers (see figs 1A and B). Electromyography (EMG) showed chronic extensive active myogenic damage and chronic inflammatory myopathy. A Computed Tomography (CT) scan revealed multiple fibrous foci in both lungs, with minor effusion in the right thoracic cavity. Electrocardiogram (ECG) revealed sinus tachycardia.

Based on the history and findings, the patient was diagnosed with SLE complicated with ITP and PAH. She demonstrated six of the 11 American College of Rheumatology criteria for diagnosing SLE. The patient was admitted in a dermatology department under management of a multidisciplinary team. Initially, the patient received 250 mg/day of intravenous pulsed methylprednisolone in 3 consecutive days, then 120 mg/day for 13 days, Immunoglobulin (20 g/d for five days), cyclophosphamide (125mg/d), mycophenolate mofetil (MMF) (1g/d), and hydroxychloroquine (400mg/d). To improve patients' cardiopulmonary function, patient was given calcium antagonists (amlodipine 20mg/d), angiotensin receptor blockers (losartan 100mg/d), an endothelia receptor inhibitor (Bosentan 250mg/d) and phosphodiesterase inhibitor (sildenafil 60mg/d). To address thrombocytopenia, the patient initially received seven units of platelets, erythropoietin (4000 IU/week), and five sessions of plasmapheresis.

After three weeks of medication, most symptoms and laboratory parameters were normalized. However, thrombocytopenia persisted (platelets count 6*10^9/L), and 24 hr urine protein was raised significantly (6135 mg/ 24hr). Vincristine 2 mg was administered. In the first week of vincristine administration, platelet levels increased significantly, and 24 hr urine protein was also improved (6135 to 558). Finally, her total SLE Disease Activity Index (SLEDAI) score was 13 (thrombocytopenia, proteinuria, myositis and urinary cast) with a physician's global assessment score of 2. The patient was discharged on a steroid taper and hydroxychloroquine and sildenafil and mofetil mycophenolate. A year later, physical, laboratory and echocardiography findings showed no sign of ITP and PAH.

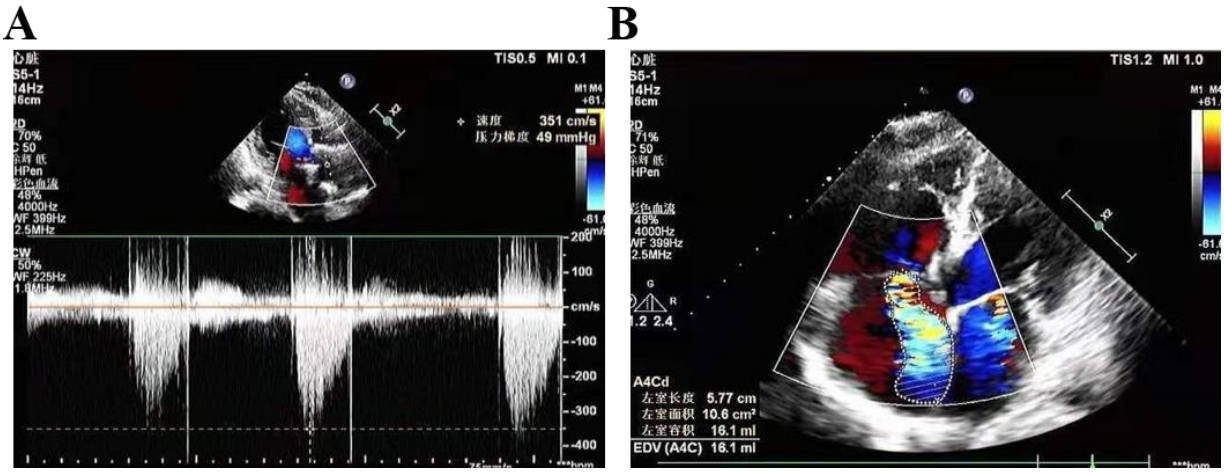

Fig. 1: Echocardiography showing pulmonary hypertension (49mmHg), normal size and structures of each cardiac cavity were normal with pulmonary hypertension (A), color flow showing tricuspid regurgitation (B).

Discussion

SLE is uncommon and frequently occurs in adolescence with a peak incidence of 0.005% per year [1]. The clinical manifestation of SLE often mimic other diseases, making it critical for clinicians to consider in-depth history taking, appropriate laboratory and preliminary examinations. SLE complicated with refractory ITP is rarely reported but it is significant due to fatal morbidity [4], with higher prevalence range between 10% to 50% [6]. Most patients with SLE with thrombocytopenia have increased peripheral destruction that is commonly mediated by anti-platelet antibodies [6]. The distinctive feature of ITP is thrombocytopenia, on peripheral blood smear, the morphology of platelets is typically normal. ITP is believed to influence PAH in SLE [4]. Recent studies provide prevalence of PAH in patients with SLE ranges from 0.5 to 43% [7]. A female predominance demographic data indicates earlier onset age in Mongoloids compared to the Caucasian patients [5].

Treatment

The mainstay of SLE treatment is glucocorticoids and hydroxychloroquine [1]. Once the patient is unresponsive to mainstay drugs or goes into remission, other definitive treatments like the biological agents and immunosuppressive drugs such as azathioprine, methotrexate, cyclosporin, mofetil mycophenolate are administered. Pathophysiologically, PAH involve endothelial cell and fibroblast dysfunction that results in impaired production of vasodilators and over- expression of vasoconstrictors. As a result, vascular tone is affected and promote vascular remodeling leading to pulmonary arterial vasoconstriction [7]. Therefore, mainstay of PAH treatment involves endothelin receptor antagonists (ERAs) drugs, nitric oxide pathway drugs, and prostacyclin drugs. Diuretics and digoxin can be added in cases of right ventricular volume overload and low cardiac output, respectively [2]. Calcium-channel blockers are indicated for patients who satisfy the criteria for a positive vasodilator response. However, closer safety and efficacy follow-ups are necessary [2]. The mainstay of ITP treatment is intravenous immunoglobulins (IVIG) and glucocorticoids [8], with a total response in 61% of cases [6]. However, more than three-quarters of adults fail to achieve a permanent response on options like colchicine, plasma exchange, dapsone, and erythropoietin-like agents [3].

Additionally, splenectomy is indicated after four to six weeks of medication though it can be delayed up to three years of ITP onset [8]. Based on the failure of first line medication for 4 weeks, a diagnosis of refractory ITP is established [3]. Concerns about the refractory ITP led us to use vinca alkaloid. The outcome improved platelet levels within a week and shortened hospitalization. Several studies showed similar response rate of 5 to 7 days [8]. In a prospective trial, 35% of patients treated with vincristine achieved a platelet count >100 × 10^9/L, but a 40% decline in the platelet count was observed 8 weeks after completion of 3 infusions [8]. In

recent findings, after completion of three infusions of vincristine, 35% of patients achieved a platelet count>100 × 10^9/L [9] within 8 weeks. Our results confirmed the efficacy of vincristine as concluded by previous studies that VAs act significantly faster than glucorticoid when used alone [10]. Due to patient's short response time, vinca alkaloid must be considered for those patients who require a rapid rise in platelet count in refractory ITP. In situations where splenectomy is considered, vincristine can be administered with similar outcome [11].

Conclusion

SLE is an autoimmune condition with many presentations and complications. Hematological manifestations of SLE are quite common. However, ITP is rare and not a common presentation of SLE. The coexistence of SLE, ITP, and PAH has a serious impact on the prognosis thus prompt diagnosis and aggressive treatment are warranted to avoid irreversible organ damages and death. The involvement of a multidisciplinary team with a vast understanding of SLE is essential for effective therapeutics. Vincristine plays a major role in the rapid normalization of platelets in ITP. Due to high cost and potential toxicities, vincristine should be restricted to refractory cases of ITP before considering splenectomy. Given the successful recovery achieved in this case, we suggest further research such as randomized controlled trials focusing on evaluating the efficacy, toxicity, and adverse effects of vincristine as a frontline drug for the management of refractory ITP.

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Conflict of interest

The authors declare no conflict of interest.

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