Pulmonary hypertension in systemic Lupus Erythematosus complicated by exposure to Dexfenfluramine

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Abstract: Pulmonary arterial hypertension (PAH) is a well recognized, albeit uncommon, complication of systemic lupus erythematosus (SLE) and is characterized histologically by the presence of onionskin thickening of small arterioles. We described a 24 year-old female with SLE, complicated by pulmonary hypertension after a six-week exposure to dexfenfluramine, who died of acute myocardial infarction complicated with pneumococcal sepsis. Autopsy demonstrated pulmonary arteriolar thickening with severe sclerosis as well as the more advanced plexiform and angiomatoid lesions. Based on these findings, we hypothesize that in this case the use of dexfenfluramine, albeit for a relatively short period, exerted a synergistic effect on the predisposition to PAH already inherent in this patient with SLE.

Key words: pulmonary arterial hypertension, SLE, plexiform lesions, angiomatoid lesions, fenfluramines

Pulmonary arterial hypertension (PAH), is a well recognized, albeit uncommon complication of systemic lupus erythematosus (SLE). In previously reported cases, the pulmonary lesions consisted only of onionskin thickening of the small arterioles (also termed concentric intimal fibroelastosis) [1]. Vasoproliferative/angiomatoid lesions and fibrinoid necrosis are the more severe histological manifestations of PAH and have not been observed in SLE. They were seen in idiopathic pulmonary arterial hypertension (IPAH; previously termed primary pulmonary hypertension) [2], and cases associated with left to right congenital cardiovascular shunts, chronic hemolytic anemia and use of appetite-suppressant medications.

We describe a case of severe PAH in a patient with SLE, who took dexfenfluramine for six weeks. Due to the severity of the histological lesions, we hypothesize that in this case dexfenfluramine exerted a synergistic effect on the predisposition to PAH inherent in this patient because of her underlying SLE.

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Case Report

The patient was a 24-year-old woman who developed idiopathic thrombocytopenic purpura (ITP) at the age of 8 years. Later, she developed leukopenia and a characteristic malar rash, leading to a diagnosis of SLE.

The ITP was resistant to corticosteroid therapy and splenectomy was performed to control the thrombocytopenia. The clinical course was further complicated by arthritis, alopecia and biopsy proven nephritis, controlled by intermittent immunosuppressive therapy. Thereafter, her SLE was relatively quiescent from age 15 through 21. At the end of that time, she took dexfenfluramine for weight loss. After 6 weeks, she developed rapidly progressive dyspnoea and persistent cough.

She presented at the Boston University Medical Center 4 weeks later. Subsequent evaluation showed an enlarged cardiac silhouette on chest radiograph. An echocardiogram demonstrated elevated pulmonary artery systolic, marked right ventricular dilatation and right ventricular volume and pressure overload.

Right heart catheterization confirmed the severe pulmonary hypertension (pulmonary artery pressure 78/34mm Hg; with a mean pulmonary artery pressure of 54mm Hg and a pulmonary vascular resistance of 1240 dynes/cm⁵). Dexfenfluramine was discontinued.

A vasodilator, prostacyclin (epoprostenol, ®Flolan), was given intravenously with marked haemodynamic and clinical response. She was maintained on epoprostenol for three and half years with further clinical and haemodynamic improvement. She subsequently suffered bouts of abdominal vasculitis requiring intermittent corticosteroid and immunosuppressive therapy. She also developed complications of steroid therapy including symptomatic coronary artery disease requiring several coronary angioplasties, placement of intra-vascular stents and eventual coronary bypass grafting.

However, she remained clinically stable until one day prior to her final admission, at which time she experienced sudden onset of fever, nausea, vomiting and diarrhea. Within eight hours, she developed signs and symptoms of sepsis and *Streptococcus pneumoniae* was isolated from blood cultures. Despite aggressive treatment with fluid resuscitation, antibiotics, vasopressive agents and mechanical ventilation, she expired shortly thereafter.

Autopsy findings

A complete autopsy was performed at the Mallory Institute of Pathology-Boston University Medical Center. The cause of death was acute myocardial infarction complicated by pulmonary sepsis.

The heart was enlarged with moderate bilateral ventricular hypertrophy. Extensive fibrosis, predominantly subendocardial, involving the left papillary muscle and multiple infarcts of varying ages were noted. The native coronary arteries showed severe obstructive stenosis but the grafts were patent. There was extensive aortic atherosclerosis and the kidneys showed lupus nephritis Grade IV.

Fifteen blocks of tissue from each lung were examined. Sections were stained with hematoxylin-eosin, Prussian blue, and elastic Van Gieson. They demonstrated the characteristic features of severe hypertensive pulmonary vascular disease: pulmonary arteriopathy with plexiform lesions [3].

Many small arteries and arterioles showed concentric fibromuscular thickening, which on elastic stain was predominantly intimal (Fig. 1).

Fig. 1 Lung tissue (Elastic Van Gieson stain x200). A small artery showing marked fibrous thickening with severe stenosis. The central lumen is less than ten percent of the total intimal area and may represent either residual lumen or recanalization. The medial elastic lamina demonstrates fragmentation, splitting and reduplication. The vessel is surrounded by angiomatoid dilatation channels.

Fig. 2 Lung tissue (Hematoxylin-Eosin stain x100). Plexiform lesion with peripheral angiomatoid dilatation channels. The dilatation channel just below the plexiform lesion is filled with fibrinous thrombotic material.

An occasional vessel was completely occluded and some had small intimal channels suggestive of recanalization. The larger medium sized muscular arteries also showed medial hypertrophy with fragmentation of the elastic lamina. Numerous plexiform, angiomatoid, and dilatation lesions were also prominent, characteristically occurring at arterial branching points, and clustering around the thickened vessels (Fig. 2). Some of the thin walled dilatation channels contained fibrinous thrombi. There was no evidence of fibrinoid necrosis, acute arteritis or diffuse pulmonary hemorrhage.

Discussion

The histological manifestations of PAH have been categorized by degree of severity in the 1975 WHO classification [4]. Low-grade lesions are characterized by “onionskin” thickening of arterioles and arteries, whereas high-grade lesions show vasoproliferative and dilatation lesions. In reported cases of PAH associated with SLE, only low-grade lesions vascular lesion have been described [1]. Our case presented with numerous high-grade pulmonary hypertensive lesions.

Pulmonary hypertension and SLE

Clinical data suggests that a “pulmonary Raynaud’s phenomenon” correlates with the development of PAH in SLE patients [1, 5]. However, a recent study indicates that pulmonary hypertension develops in patients with SLE as result of abnormal inflammatory reaction which affects the blood vessels. This is characterized by endothelial dysfunction associated with increased level of vascular endothelial growth factor, sP-Selectin, and lipoprotein-associated phospholipase A2 [6].

Others consider pulmonary hypertension in SLE, as a multi-hit process where a gene alteration is followed by a circumstantial condition. Lang et al (2003) suggest that these patients are characterized by mutations of the bone morphogenetic protein receptor 2 (BMP2) genes and activin-receptor like kinase 1 gene which would affect the transforming growth factor beta receptor involved in the regulation of growth [7].

Pulmonary hypertension and Fenfluramine

Pulmonary hypertension represents a side effect in some people who have taken fenfluramine and similar anorectic agents over extended periods of time [8]. In these individuals the ability to metabolize the drug might be impaired but this is not sufficient to explain the subsequent pulmonary vasoconstriction. However, studies performed on transgenic rats have revealed that pulmonary hypertension induced by dexfenfluramine, the active ingredient of fenfluramine is dependent on the peripheral level of serotonin [9].

Also, dexfenfluramine induces vasoconstriction through its metabolite, nordexfenfluramine which activates the 5-HT₂ receptors. Nordexfenfluramine increases the cytosolic calcium concentration in pulmonary artery smooth muscle cells by promoting the influx of extracellular calcium and the release of calcium from sarcoplasmic reticulum. [10].

Archer et al [11] have claimed that fenfluramine becomes a pulmonary vasoconstrictor after suppression of the synthesis of the natural endogenous vasodilator, nitric oxide. Thus, in some people, endogenous nitric oxide deficiency might explain their preferential susceptibility to develop pulmonary hypertension when exposed to anorectic drugs.

Another clinical study performed in patients with pulmonary hypertension after taking fenfluramine showed that 9% of cases are characterized by several bone-morphogenetic protein receptor 2 (BMP2) gene mutations. Surprisingly, these patients had a shorter duration of exposure to fenfluramine compared with mutations-negative patients [12].

Pulmonary hypertension, SLE and Fenfluramine

Regarding the combined effects of fenfluramine and SLE, it appears reasonable to speculate that pulmonary vessels in chronic SLE, possibly damaged by deposition of immune complexes, are particularly susceptible to the vasoconstrictive effects of serotonin released by exposure to fenfluramine [13]. Interestingly, alterations of BMPR2 gene leading to pulmonary hypertension have been described in both patients with SLE and in those taking fenfluramine [7, 12]. Therefore, one may speculate that BMPR2 is crucial in pulmonary hypertension pathogenesis regardless of the background of the patient.

In classic primary pulmonary hypertension (now termed IPAH), the most distinctive histological abnormality is the plexiform lesion. It is widely accepted that as pulmonary blood pressure increases, the muscular layer of the pulmonary arterial branches becomes weak and incompetent. This may result in the formation of dilatation or aneurysmal lesions, which may be "vein-like branches" of thin-walled blood vessels.

Thus, a plexiform lesion is a complex structure made of a plexus of capillary-like channels within a short dilated segment of arteriole close to its origin from a larger main artery. The cells within the plexus appear to be a mixture of smooth muscle cells, myofibroblasts and endothelial cells [3]. Occasionally, there is fibrinoid necrosis and platelet agglutination, in which case it is important to distinguish the plexogenic lesions from microthrombi. As a result of the necrosis, elastic laminae may be interrupted or destroyed.

The muscular hypertrophy observed in this case has been described by Wagenvoort [14] in patients with IPAH as a muscularization of the arterioles and includes the above-mentioned features as well as the extension of smooth muscle cells along previously non-muscularized vessels. However, the rapid appearance of the high-grade morphological features described in our case may be related to both the severity and duration of the SLE, which had been present for at least ten years, as well as the transitory exposure to fenfluramine

Although exceptionally rare, at least some cases of PAH are reversible, both clinically and anatomically. The low-grade lesions with the exception of severe concentric laminar intimal fibrosis are reversible, whereas the high-grade lesions are irreversible. In PAH due to ingestion of anorectic agents there are rare cases of recovery after withdrawal of the medication. Majority of the cases progress even if the drug has been terminated [15]. These observations suggest that once lesions have progressed beyond a certain point, they become irreversible.

In conclusion, this case represents a unique example of high-grade pulmonary hypertensive vascular disease developed in a patient with SLE after a short exposure to dexfenfluramine. Given their serious side-effects the anorectic agents such as fenfluramine have no use in today's clinical practice.

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