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Primary Systemic Vasculitides as a Cause of Group IV Pulmonary Hypertension

ABSTRACT

The primary systemic vasculitides are rare diseases characterized by vessel wall inflammation. Isolated pulmonary vasculitis, large-vessel vasculitis, and Behçet's disease are mimickers of chronic thromboembolic pulmonary hypertension (CTEPH); group IV pulmonary hypertension (PH) can occur as a devastating complication in the course of these diseases. Pulmonary endarterectomy, balloon angioplasty, anticoagulation and pulmonary vasodilator agents are the main treatment options for CTEPH. There is no specific recommendation for the treatment of patients having group IV PH due to primary systemic vasculitides. We reviewed herein data about group IV PH due to primary systemic vasculitides.

Keywords: Behçet's disease, group IV PH, primary systemic vasculitides, Takayasu arteritis

REVIEW

INTRODUCTION

The primary systemic vasculitides are a rare group of heterogeneous diseases characterized by vessel wall inflammation. Overall, the estimated annual incidence of primary systemic vasculitides is >100 new cases per million.[1] The prevalence of various types of primary systemic vasculitides differs by age, gender and geographical region. Giant cell arteritis (GCA) is a disease of the elderly above the age of 50, while Kawasaki disease is a vasculitis of childhood. Takayasu arteritis (TA) mostly affects young women. Microscopic polyangiitis is more common in Asia, whereas granulomatosis with polyangiitis is more frequently seen in Western populations.[2,3] The vasculitides had been categorized during the 2012 International Chapel Hill Consensus Conference by using their features; such as the size of vessels involved, the pathogenesis or the etiology (Table 1).[2] Secondary vasculitides are listed in the category with known etiology or associated with systemic diseases; others are considered primary vasculitides.[2] Although each vasculitis has distinct organ involvement patterns and typical pathological features, it can mimic almost any disease. Therefore, the diagnosis of a vasculitis is challenging in most cases and should be supported pathologically whenever possible.[3] Tissue ischemia due to occluded or narrowed arteries, aneurysm formation and hemorrhages are the main causes that can lead to organ dysfunction in the course of vasculitis. Frequent disease flares and the need for long-term immunosuppressive treatment are other two important conditions that physicians have to overcome to preserve organ functions.

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure >20 mm Hg at rest with right heart catheterization.[4] A variety of causes can lead to PH. Pulmonary hypertension is not a disease itself but can rather be defined as a clinical condition like anemia. The causes of PH are classified into 5 groups (Table 2).[4,5] Left heart diseases (LHD) are the most common causes of PH followed by lung diseases.[4,5] Regardless of its cause, the presence of PH is considered a poor prognostic factor. Interest in PH has increased after pulmonary arterial hypertension (PAH)-specific agents have been proven to be effective in group I PH patients. In group I PH or in other words, in PAH, proliferative remodeling in the precapillary arterioles leads to the development of PH by increasing pulmonary

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Table 1. Names of Vasculitides Adopted by the 2012 International Chapel Hill Consensus Conference Nomenclature of Vasculitides

Large-vessel vasculitis
Takayasu arteritis
Giant cell arteritis
Medium-vessel vasculitis
Polyarteritis nodosa
Kawasaki disease
Small-vessel vasculitis
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis
Microscopic polyangiitis
Granulomatosis with polyangiitis (Wegener's)
Eosinophilic granulomatosis with polyangiitis (Churg Strauss)
Immune complex small-vessel vasculitis
Anti-glomerular basement membrane disease
Cryoglobulnemic vasculitis
Ig A vasculitis (Henoch–Schönlein)
Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)
Variable-vessel vasculitis
Behçet's disease
Cogan's syndrome
Single-organ vasculitis
Cutaneous leukocytoclastic angiitis
Cutaneous arteritis
Primary central nervous system vasculitis
Isolated aortitis
Others
Vasculitis associated with systemic disease
Lupus vasculitis
Rheumatoid vasculitis
Sarcoid vasculitis
Others
Vasculitis associated with probable etiology
Hepatitis C virus-associated cryoglobulinemic vasculitis
Hepatitis B virus-associated vasculitis
Syphilis associated vasculitis
Drug-associated immune complex vasculitis
Drug-associated ANCA vasculitis
Cancer-associated vasculitis
Others

Table 2. Clinical Classification of Pulmonary Hypertension

Group 1 Pulmonary arterial hypertension
Group 2 Pulmonary hypertension due to left heart disease
Group 3 Pulmonary hypertension due to lung diseases and/or hypoxia
Group 4 Pulmonary hypertension due to pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
4.2.1 Sarcoma (high or intermediate grade) or angiosarcoma
4.2.2 Other malignant tumors
Renal carcinoma
Uterine carcinoma
Germ cell tumors of the testis
Other tumors
4.2.3 Non-malignant tumors
Uterine leiomyoma
4.2.4 Arteritis without connective tissue disease
4.2.5 Congenital pulmonary artery stenoses
4.2.6 Parasites
Hydatidosis
Group 5 Pulmonary hypertension with unclear and/or multifactorial mechanisms

HIGHLIGHTS

- Pulmonary artery involvement of primary systemic vasculitides can lead to group IV pulmonary hypertension (PH) and mimic chronic thromboembolic pulmonary hypertension (CTEPH).
- Group IV PH is an important cause of mortality in primary systemic vasculitides.
- Immunosupressives are the mainstay treatment for systemic vasculitides. Pulmonary vasodilator agents, balloon angioplasty and pulmonary endarterectomy are effective treatment options in CTEPH that may also be useful in carefully selected patients with primary systemic vasculitides with group IV PH.

vascular resistance (PVR).[4,5] Despite all impressive advances in the treatment of PAH, chronic thromboembolic pulmonary hypertension (CTEPH) is still the only curable PH type.[4,5] Any type of PH can be seen in vasculitides. The involvement of major organs such as the heart, lung or kidney can lead to PH development. Patients with vasculitis are at increased risk for thrombosis; consequently, CTEPH can also occur in the disease course.[6,7] Even cases with PAH due to probable small-vessel vasculitis without prominent heart or lung dysfunction have been reported among patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, Kawasaki disease and immunoglobulin A vasculitis.[7-9] However, vasculitides, along with other CTEPH mimickers, are listed separately under group IV causes of PH.[5] The definition of "arteritis without connective tissue disease" was made likely to exclude patients with both secondary and small-vessel vasculitis. Isolated pulmonary vasculitis (IPV), large-vessel vasculitis and Behçet's disease (BD) are the primary systemic vasculitides that best fit this definition. There are no specific recommendations for the treatment of patients with group IV PH due to systemic primary vasculitides.[4,10,11] We reviewed herein data about group IV PH due to primary systemic vasculitides.

ISOLATED PULMONARY ARTERY VASCULITIS

Single-organ vasculitides are the least frequent type of vasculitides. In single-organ vasculitides, there are no signs and symptoms related to organ systems other than the involved organ. Localized or diffuse arterial or venous vasculitis can be detected in the affected organ, such as primary central nervous system vasculitis, isolated cutaneous arteritis or testicular vasculitis. The diagnosis of the patients may evolve into one of the primary systemic vasculitides types by addition of typical symptoms or signs associated with different organ involvements over time. Therefore, close follow-up is warranted in these patients.[2]

Isolated pulmonary artery vasculitis (IPV) is very rare; there were only a few cases reported in the literature.[12,13] It has been reported that among 200 patients who underwent pulmonary endarterectomy operation (PEA), only 2 patients were diagnosed as IPV.[14] Large-, medium-, or small-sized pulmonary artery involvement (PAI) can be seen in the course of the disease. Diffuse pulmonary hemorrhage (DPH) due to capillaritis is the most common manifestation of the small-vessel PAI.[15] Patients with main, lobar, segmental or subsegmental pulmonary arterial involvement may be asymptomatic or suffer from dyspnea and/or chest pain. Isolated pulmonary artery vasculitis with large or medium PAI can cause PH (group IV PH) and mimic CTEPH.[12-15] Many patients with IPV had suspicious lesions in systemic arteries or autoantibody positivity.[12-14] Therefore, these patients should be followed up closely as should the ones with single-organ vasculitis. Significant thickening and/or contrast enhancement in the pulmonary arterial walls are typical for the diagnosis of vasculitis.[16] Elevated serum acute phase reactants or the presence of chronic disease anemia are nonspecific but easily accessible parameters for a rapid evaluation. The evaluation of these patients should also include imaging of other systemic vessels. Immunosuppression is the mainstay therapy.[15] It has been suggested that PEA can be used both for the diagnosis and treatment of IPV patients with PH.[17] Although PEA can be a treatment option in resistant cases, the diagnostic utility of this approach is debatable. First of all, surgery can be detrimental to these patients unless inflammation is properly controlled. Secondly, since the specimens of PEA contain mainly the intima layer of the arteries, they will be largely insufficient for diagnosis.[18] Indeed, the presence of vasculitis could not be documented in BD patients who underwent PEA.[19] Moreover, acute or chronic inflammatory cell infiltration of the pulmonary arteries is not specific for vasculitis and can be seen in half of the patients with CTEPH.[18]

TAKAYASU ARTERITIS

Takayasu arteritis is a granulomatous large-vessel vasculitis of unknown etiology, characterized by the involvement of aorta and its branches. It usually affects young women <40 years old.[20] Takayasu arteritis is a panarteritis with typical pathological findings including inflammatory cell infiltration, neovascularization, internal elastic lamina fragmentation, granuloma formation in the media layer and intimal hyperplasia. Arterial wall fibrosis is a feature of inactive, old lesions.[3,21] Takayasu arteritis is considered to be a slowly progressive disease; most of the patients have only constitutional symptoms such as low-grade fever, unintentional weight loss or fatigue during the initial-early phase. In the late phase, ischemic symptoms such as extremity claudication, dizziness or angina may occur due to narrowing of arteries. Decreased arterial pulses, blood pressure asymmetry between extremities or bruits on the arteries are signs of the late phase, while tenderness on the arteries can be an earlier sign.[10,20,21] Takayasu arteritis diagnosis mainly depends on imaging of the aorta and its branches (by magnetic resonance angiography (MRA) and/or computerized tomography angiography (CTA) and/or conventional angiography), since tissue sampling from arterial lesions is not feasible except for the cases who underwent vascular surgery.[10,20,21] Arterial wall thickening and irregularities, stenoses, occlusions, aneurysms and the presence of collateral vessels are the typical findings of TA.[16,20,21] Besides the aorta, the subclavian and common carotid arteries are the most frequently involved vessels in TA.[20,21] Multiple and long-segment arterial lesions are supportive of TA diagnosis.

Heart failure, stroke and cerebral hemorrhage are the major causes of mortality in TA.[10,20] Overall survival at 15 years is 85%.[10] The presence of renal arterial stenosis, aortic regurgitation and aortic or arterial aneurysms were suggested as poor prognostic factors.[3] In the last decade, PAI and PH emerged as 2 additional important conditions related to TA mortality.[22,23]

Pulmonary Arterial Involvement in Takayasu Arteritis

The prevalence of PAI in TA has been reported to be between 6% and 66% in different series.[20,23-27] Although PAI is considered to occur in the late phase of the disease, it can be detected at presentation and may be the initial and the sole manifestation of TA.[20,25,28] Dyspnea, hemoptysis, chest pain, syncope and extremity edema are symptoms of PAI; however, TA patients with PAI may also be asymptomatic.[23-25] Pulmonary arterial involvement can be overlooked in asymptomatic cases or misdiagnosed as CTEPH. Therefore, clinicians should request imaging reports that comprise adequate information about pulmonary circulation. Takayasu arteritis patients' evaluation is incomplete without data about pulmonary circulation. In some studies, the involvement of segmental and/or subsegmental pulmonary arteries was reported to be more frequent than the larger arteries.[20,25] However, recent data indicate a significant rate of involvement in the main and lobar pulmonary arteries.[23,29] Although bilateral PAI is common, the overall right pulmonary artery and its branches are affected more frequently than the left-sided ones. Occlusions and stenoses of pulmonary arteries are the most common lesions; aneurysms are rare and collateral vessels can be seen (Figure 1).[16,23,25,30] In situ thrombus formation has been reported in up to 8% of the cases.[24] The rosary-like appearance due to sequential stenosis and dilatation of the pulmonary arteries is typical for TA.[30] Male gender and long disease duration are associated with an increased frequency of PAI.[20,25,28] The frequency of nontuberculous mycobacteria infection was found to be higher in patients with PAI as compared to those without.[24,25] Patients with PAI reported to have less abdominal aortic and renal artery involvement.[23-25] Finally, PH, which is associated with mortality, is more common in patients with PAI than those without.[23,25,27]

Group IV Pulmonary Hypertension in Takayasu Arteritis

Pulmonary hypertension is a severe complication of TA, and its prevalence is reported to be 2.4-43% of the patients, depending on the diagnostic method used.[20,23-27] Pulmonary hypertension due to PAI, in other words, group IV PH, is the most common type of PH reported in TA.[23,25] Approximately half of the patients with PAI are considered to have PH. Other than group IV PH, hypertensive heart disease, ischemic heart disease, valvular disease and myocarditis are the

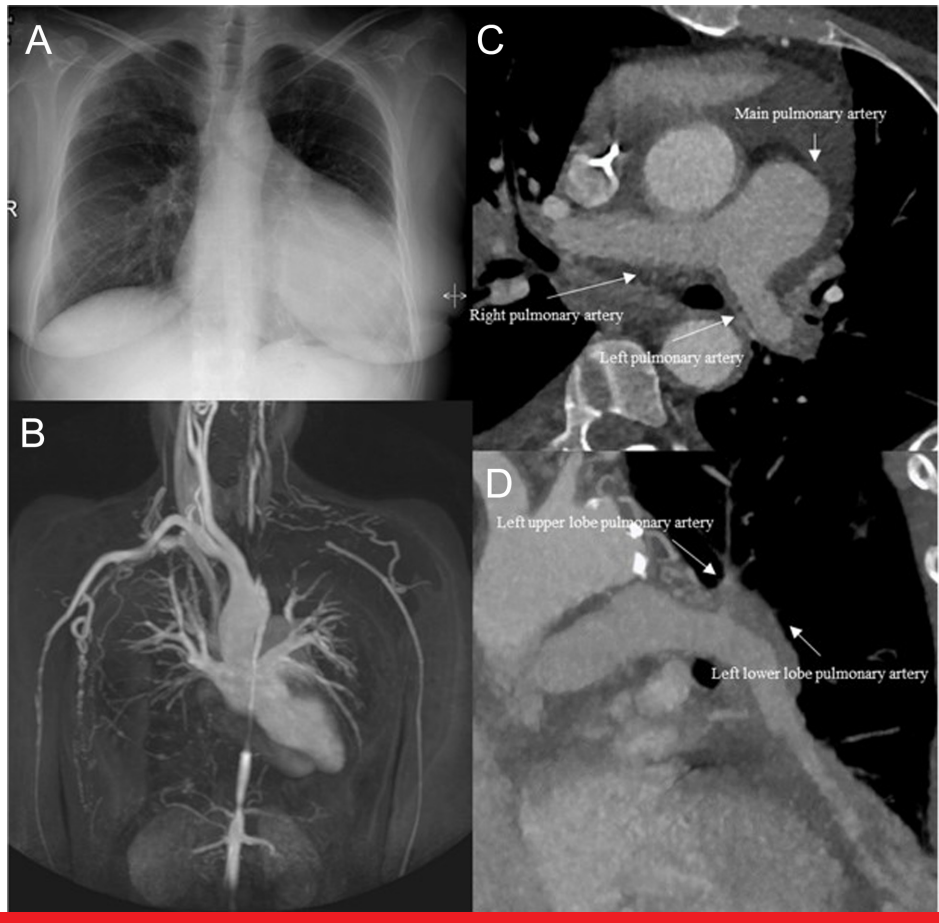

Figure 1. Imaging findings of patients with Takayasu arteritis and group IV pulmonary hypertension: (A) cardiomegaly; (B) systemic arterial involvement and collateral vessels; (C) dilatation of the main pulmonary artery, wall thickening and luminal narrowing in right and left main pulmonary arteries; and (D) wall thickening in both the left upper lobe and left lower lobe pulmonary arteries; subtotal occlusion in the left upper lobe pulmonary artery.

conditions that can lead to group 2 PH (due to LHD) in TA.[23,31] It has been reported that 30% of the patients with PAI had also significant LHD.[23] The volume status of the patients with renal failure should also be kept in mind in TA patients with PH. Therefore, in patients with PAI, defining the exact cause of PH can be challenging.

Mechanical obstruction of the pulmonary arteries is the main mechanism for the development of PH in patients with PAI. Most of the TA patients with group IV PH have multiple bilateral pulmonary artery occlusions.[23,25,29] A significant correlation between pulmonary artery pressures and the extent of PAI has been documented.[23] Vasculopathy of the small vessels due to altered blood flow in pulmonary circulation is considered a contributing factor for the development of PH in CTEPH.[4,5,32] Vascular abnormalities distal to the occluded arteries have been shown in TA patients.[10,33] On the other hand, the progression of PAI was not observed during the follow-up of all TA patients with PH.[34] Therefore, like CTEPH, small-vessel vasculopathy can be another important cause for the development of PH in TA patients with stable pulmonary arterial lesions. Similarity in the diameters of involved pulmonary arteries has been documented between CTEPH and TA patients.[32] Hypoxia, systemic to pulmonary shunts, endothelial dysfunction, small-vessel vasculitis and neurohumoral activation are other potential factors that may contribute to the development of PH in TA.[27-29]

Patients with TA and group IV PH have a poor prognosis. These patients were suggested to have more severe PH as compared to patients with idiopathic PH, as they have a lower cardiac index despite similar systolic pulmonary artery pressures.[29] Pulmonary hypertension related complications, right heart failure and sudden cardiac death were found to be the leading causes of mortality in TA patients with group IV PH. The overall 1-, 3-, and 5-year survival rates of the patients were reported to be 94%, 82%, and 77%, respectively. In the same study, the factors associated with an increased risk of all-cause death were syncope, an increased N-terminal pro-B-type natriuretic peptide (NT-proBNP) level and elevated mean right atrial pressure.[22] He et al[23] reported a 7-fold higher mortality rate in patients with PAI and PH as compared to those without PH in TA. In their study, disease duration, New York Heart Association class III/IV, right ventricular systolic dysfunction and respiratory failure were suggested as independent predictors of mortality. In addition, PH patients with both PAI and LHD had the worst prognosis.[23]

Treatment of Group IV Pulmonary Hypertension in Takayasu Arteritis

Planning treatment for TA patients with group IV PH is challenging; evaluation of these patients should be performed by a multidisciplinary team including internists, cardiologists, pulmonologists, rheumatologists, radiologists and cardiovascular surgeons (Figure 2).

Immunosuppressive treatment is the mainstay therapy to control inflammation in TA. Steroids are the first choice to induce disease remission. Concomitant immunosuppressive agents such as methotrexate, azathioprine or mycophenolate mofetil are recommended in order to prevent disease flares and steroid side effects over the long term. Cyclophosphamide or biologic treatments [tumor necrosis factor (TNF)-α antagonists, tocilizumab] are used for severe or resistant cases.[10,21] It has been reported that TA patients with PAI have a more severe disease course than those without.[25] The number of TA patients who were treated with cyclophosphamide or biologic agents was found to be higher in patients with PAI compared to patients without.[27] However, in a recent study performed with 140 TA patients with group IV PH, 40% were not on immunosuppressive treatment.[22] Takayasu arteritis patients in long-term remission do not need aggressive immunosuppressive treatment. Immunosuppressive agents are associated with an increased risk of infections that can have disruptive effects on fragile patients such as TA patients with PH.[24] Therefore, although the assessment of disease activity is challenging in TA, the evaluation of TA patients with group IV PH should be done attentively for the need of immunosuppressive treatment. Moreover, despite the fact that immunosuppressive treatment is effective in controlling inflammation and the occurrence of new vascular lesions, regression of occlusive or stenotic vascular lesions is rare.[21] It is clear that additional treatments are needed in TA patients with group IV PH.

Vasodilators are effective both in group I PH and CTEPH.[4] In a study, a vasoreactivity test was found positive in all 48 TA patients with group IV PH, and symptoms improved after treatment with calcium channel blockers.[29] The number of TA patients with group IV PH who were treated with PAH-specific agents has been increasing despite a lack of randomized control trials about their efficacy.[22,29] Although any kind of PAH-specific agent has been used for the treatment as monotherapy or in combination, there is more experience with oral agents targeting endothelin (bosentan) and nitric oxide (sildenafil) pathways than agents effective on the prostaglandin pathway.[22,29] Improvement in NT-proBNP levels and hemodynamic parameters was reported in TA patients with group IV PH after treatment with PAH-specific agents.[22] The response to PAH-specific

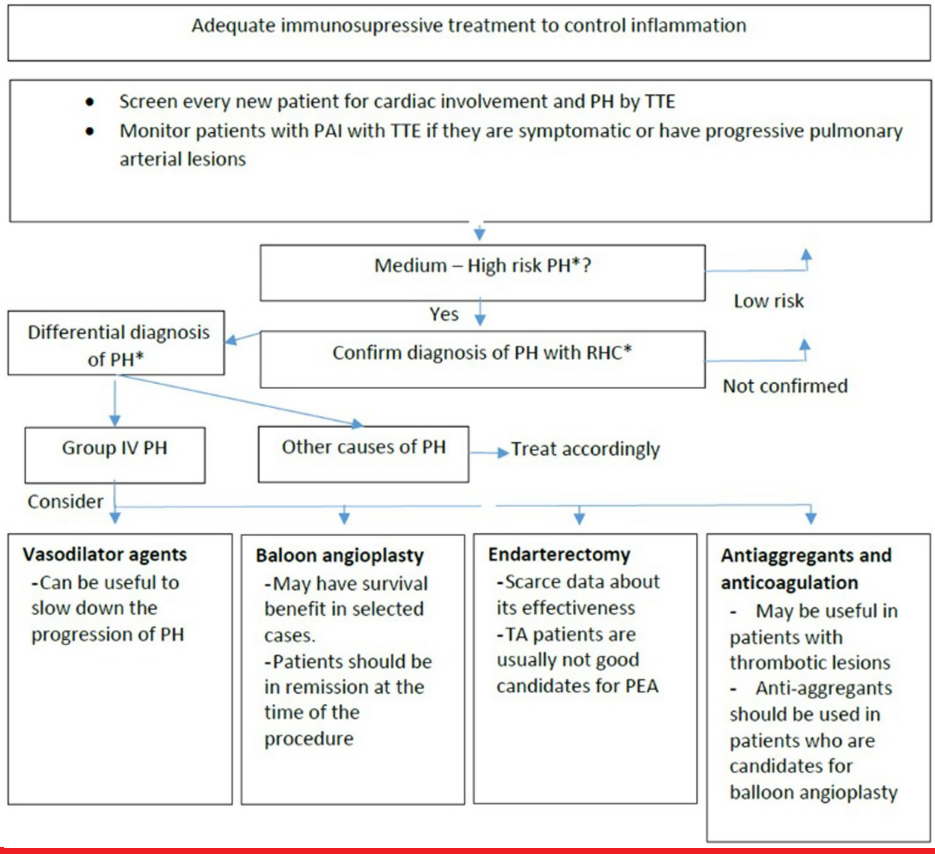

Figure 2. Treatment algorithm for Takayasu arteritis patients with group IV Pulmonary hypertension. *According to 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. PH, pulmonary hypertension; TTE, transthoracic echocardiography; PAI, pulmonary arterial involvement; RHC, right heart catheterization; TA, Takayasu arteritis; PEA, pulmonary endarterectomy.

agents supports the important contribution of small-vessel vasculopathy to PH, while revascularization should still be the primary goal of treatment. Current guidelines do not recommend a vasoreactivity test in group IV PH.[4] The impact of the vasoreactivity test for drug selection and the efficacy of combination vasodilator agents remain to be further explored.

Pulmonary endarterectomy is still the first choice of treatment in CTEPH.[4,5] Balloon angioplasty is recommended in CTEPH patients who are not suitable for PEA or have persistent/recurrent PH after the operation.[4] Although successful endarterectomy operations in systemic arteries have been reported in TA, data about PEA is limited.[34] Takayasu arteritis patients with group IV PH who have distal pulmonary artery involvement are not good candidates for PEA. Moreover, in these patients, occlusion or stenosis of the pulmonary arteries are mediated by inflammation rather than thrombosis, which may increase the complication rate of PEA. Another concern is the high recurrence rates in TA after surgery as compared to atherosclerosis.[34] Experience with vascular interventions is increasing despite having similar limitations with PEA. Reperfusion lung injury, bleeding and early recurrence of lesions are the major complications of vascular interventions.[23,29,35] Currently, with the improvement in interventional techniques and post-procedure patient care, these treatment options seem to have acceptable complication rates. Recently, Huang et al[35], compared the outcomes of endovascular (n = 54) and medical treatment (n = 75) in TA patients with group IV PH over a mean follow-up period of 55 months; they reported pronounced improvement in both hemodynamic and clinical parameters in the intervention group as compared to the medical treatment group. Moreover, the intervention group had significantly lower rate of mortality than the medical treatment group.[35] As with any revascularization intervention or surgery, TA patients who are candidates for balloon angioplasty should be in remission. Adequate antiaggregant treatment is important during the peri-procedural period to prevent recurrences.[35]

It is clear that PH develops as a consequence of the progression of pulmonary arterial lesions in most TA patients. Accordingly, early immunosuppressive treatment and timely escalation of therapy in the course of the disease may prevent the development of PH in TA. Young TA patients with PAI are at increased risk of having active disease. The presence of chest pain, increased platelet count and pulmonary artery wall thickening were reported to be associated with the disease activity of PAI.[36] New imaging techniques such as somatostatin receptor 2 positron emission tomography and magnetic resonance imaging, may provide additional information about the activity of disease.[37] A mean lag period of 2 years was reported between symptom onset and diagnosis of PH in TA patients with PAI.[22] Screening TA patients with PAI for the presence of PH by echocardiography and early initiation of PAH-specific agents may slow down the progression of PH. The effectiveness of early revascularization on the prognosis of these patients awaits further investigation, as in patients with chronic thromboembolic disease.[4]

GIANT CELL ARTERITIS

Patients with GCA are usually evaluated for symptoms or signs associated with the involvement of extracranial branches of the carotid arteries at the time of diagnosis. Vision loss is the well-known and most-feared complication of the disease.[3,15] Involvement of the aorta and its branches is seen in 40%-65% of the patients, and aneurysm formation is an important cause of mortality. On the other hand, most of the patients are asymptomatic in this regard.[38] Although pulmonary artery involvement has been documented pathologically, DPH or PH are very rarely reported in GCA.[15] In 2 previous studies conducted to define the types of pulmonary involvement in GCA, which enrolled 219 and 678 patients, there were no patients diagnosed with PH.[39,40] There are differences in terms of the structure of arteries, blood flow and innervation between pulmonary and systemic circulation. The lack of antigens in the pulmonary arteries, which are targets for GCA, or the preventive effect of initiating immunosuppressive treatment earlier in GCA than in TA due to the acute onset of the disease may explain the very low incidence of PH in GCA. On the other hand, as GCA is a disease of the elderly, these patients have many comorbidities, including cardiac and pulmonary diseases.[3,38,39] Therefore, in the presence of PH in these patients, causes other than group IV PH, such as cardiac and pulmonary diseases, should be carefully investigated.

BEHÇET'S DISEASE

Behçet's disease is classified as a variable-vessel vasculitis that involves vessels of any size.[2] Behçet's disease was first described as a triple-symptom complex including oral aphthae, genital aphthae, and uveitis. The disease has a wide range of manifestations, ranging from self-limiting mucocutaneous lesions to vascular, central nervous system or gastrointestinal system involvement that can cause serious morbidity and mortality.[41] Unlike other primary vasculitides, the prevalence of venous involvement is significantly higher than arterial involvement in BD.[41,42] Pulmonary arterial aneurysm formation is a well-known type of vascular involvement associated with mortality in BD. PAI can also lead to the development of PH.[41,42]

Pulmonary Arterial Involvement In Behçet's Disease

The prevalence of PAI is 1%-3% in BD.[43,44] Hemoptysis, dyspnea, cough, fever and chest pain are the most frequent symptoms of PAI.[15,43,44] Although rare, the frequency of PAI may be higher than expected because there is no recommended screening strategy for PAI in BD, and PAI may exist in patients without pulmonary manifestations. Pulmonary artery aneurysms (PAA) and pulmonary artery thrombosis (PAT) are the main lesion types (Figure 3). They tend to be multiple and involve the lower lobes of the lungs. Right-sided locations are more common for PAA. Male patients are at increased risk for the occurrence of PAI.[45,46] Up to 60%-70% of the patients with PAI have other types of vascular involvement, including deep venous thrombosis, cardiac thrombosis or central nervous system thrombosis.[42-44] Although PAA is highly characteristic for BD, PAT prevalence is reported to be significantly higher than PAA in the latest studies.[44,45]

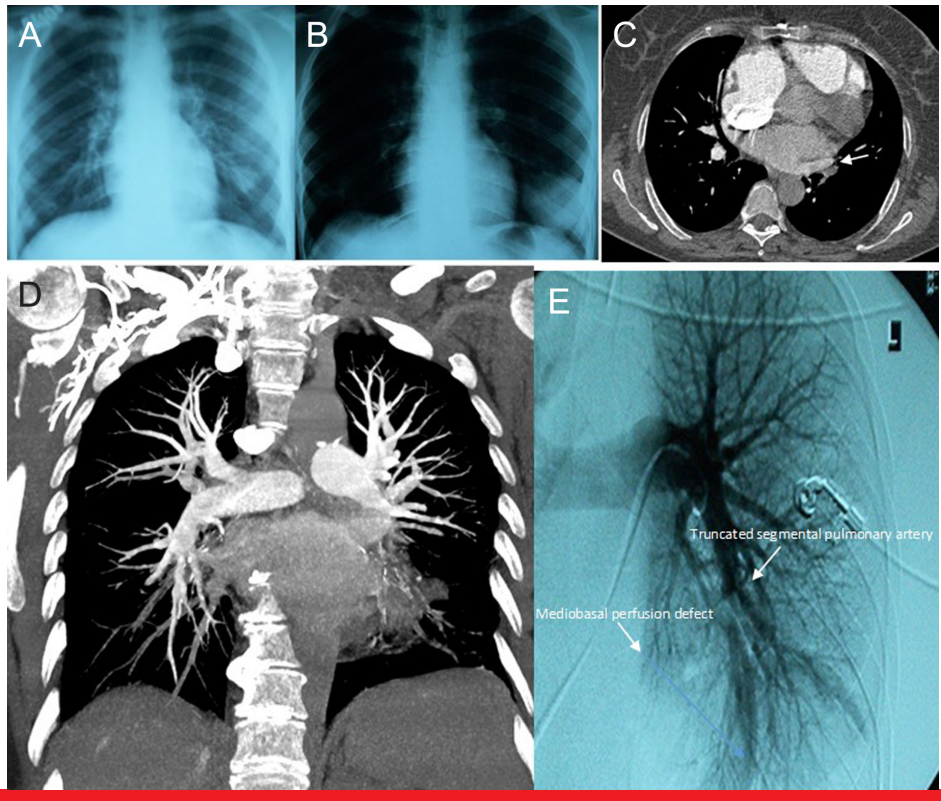

Figure 3. Imaging findings of pulmonary involvement in patients with Behçet's disease: A) pulmonary artery aneurysm; B) image of aneurysm after bleeding in the same patient; C) occlusion of basal segmental branch of left lower lobe pulmonary artery (arrow); D) coronal maximum intensity projection (MIP) reformat image shows no filling of left lower lobe basal segment arteries, calibration of right basal segment arteries are decreased and distal branches are depleted; E) multivessel involvement in pulmonary angiography.

Pulmonary infarcts, ground-glass opacities, consolidations and cavities are other types of pulmonary lesions that can be encountered in the course of the disease.[43,44]

Thrombosis is a characteristic of both venous and arterial lesions in BD. Inflammation of the vessel wall is the main mechanism for thrombus formation. In addition, activation of the coagulation system and defects in the fibrinolytic system may contribute to the development of thrombosis.[41,42] In contrast to the classical venous thromboembolic disease, thromboses in BD are considered to be tightly adherent to the vessel wall, and embolic events are rare.[41,42] Therefore, PAT lesions in BD occur due to the vasculitic process rather than embolism. Pulmonary artery thrombosis lesions may lead to the development of PAA. Massive pulmonary hemorrhage is the most important cause of mortality in BD patients with PAI, mainly due to the rupture of PAA. The mortality rate in BD patients with PAI was about 25% in earlier studies. The recurrence of PAI can be seen in about one-fifth of the cases.[43] Most of the patients with PAI are highly responsive to immunosupressive treatment.[43-45] Although the pathogenesis of PAT and PAA are similar and they can coexist, the prognostic significance of isolated PAT has not been clearly defined yet. A prominent increase in the survival rate of BD patients with PAI has been reported in recent studies, where the number of cases with isolated PAT were higher than cases with PAA.[44,45]

Huges–Stovin syndrome is characterized by the presence of both pulmonary aneurysms and deep venous thrombosis similar to BD. Most of the cases of Huges–Stovin syndrome are reported from Western countries. These patients are also at increased risk of developing PH.[46]

Group IV Pulmonary Hypertension in Behçet's Disease

The prevalence of PH in BD has been reported around 10%.[47,48] Patients with vascular involvement, mainly with PAI, are at higher risk for the development of PH.[47,48] Group IV PH is the main cause of severe PH.[19,48] Pulmonary hypertension due to LHD can also occur in patients with BD. However, the impact of BD on patients who develop LHD is controversial.[31,48] Pulmonary arterial hypertension (group I PH) can potentially occur in patients with Budd–Chiari syndrome, with small-vessel vasculitis, or due to drugs (interferon-α, cyclophosphamide) in BD.[4,41,48] On the other hand, this situation seems unlikely since there were no reported cases of BD and PH, leading to right heart failure in a short period without PAI. No association was found between PH and interferon-α treatment.[48]

Similar to TA, pulmonary artery occlusions are the main cause of group IV PH in BD. Vasculopathy of small vessels due to blood flow changes in pulmonary circulation can be an additional factor in the development of PH in the late phase.[4,19,48] Systemic to pulmonary shunts and compression of pulmonary arteries by aortic aneurysm are the other

conditions that can contribute to the development of group IV PH in BD.[48,49]

Data about the clinical follow-up of the BD patients with group IV PH are limited. Group IV PH can be seen at presentation and its presence is associated with a poor prognosis.[43] Since the presence of severe PH is a feature of CTEPH rather than massive pulmonary thromboembolism, the coexistence of both PAI and PH in BD patients at presentation suggests that patients with PAI can have a significant long-term asymptomatic period before diagnosis.[4] Group IV PH can also be detected in the later course of the disease in patients with PAI. Persistence of elevated systolic pulmonary artery pressure and scintigraphic perfusion defects has been reported in BD patients with PAI.[43] Symptoms or signs associated with right heart failure, mainly dyspnea, should alert the clinicians for the presence of PH. Recurrent hemoptysis in a patient with PAI can be a sign of group IV PH due to bleeding from bronchial arterial collaterals.[45,50] Therefore, screening and monitoring BD patients with PAI for the presence of PH should be considered.

Treatment of Group IV Pulmonary Hypertension in Behçet's Disease

Since the clinical experience for the treatment of patients with BD and group IV PH is limited, the evaluation of these patients by a multidisciplinary team is crucial, like in TA. Overall, treatment strategy should encompass the expertise from immunosuppressive treatment to endovascular interventions and surgery (Figure 4).

High-dose steroids and cyclophosphamide are the first-choice treatments for BD with PAI.[11] Treatment with anti-TNF agents (mostly infliximab) is another option.[45] Opposite to TA, regression and even disappearance of pulmonary vascular lesions can be achieved with immunosuppressive treatment only. Radiologic recovery in 70% of the PAA lesions was reported after a mean duration of a 10-month immunosuppressive treatment.[43]

Pulmonary endarterectomy has been suggested to be an effective treatment option in BD patients with group IV PH.[19] In a case series of BD with group IV PH including 9 patients, the authors reported that 1 patient died, 1 patient had pneumonectomy and 1 patient had residual PH after PEA.[19] There are no criteria for BD patients with group IV PH to determine the suitable candidates for PEA. Current guidelines recommend PEA in symptomatic CTEPH patients after adequate anticoagulation for at least 3 months.[4] Since most of the BD patients with PAI have active disease at diagnosis, the consequences of anticoagulant treatment or surgery can be detrimental in these patients. Anticoagulants can significantly increase the risk of bleeding and surgery can aggravate inflammation.[43,44,49]

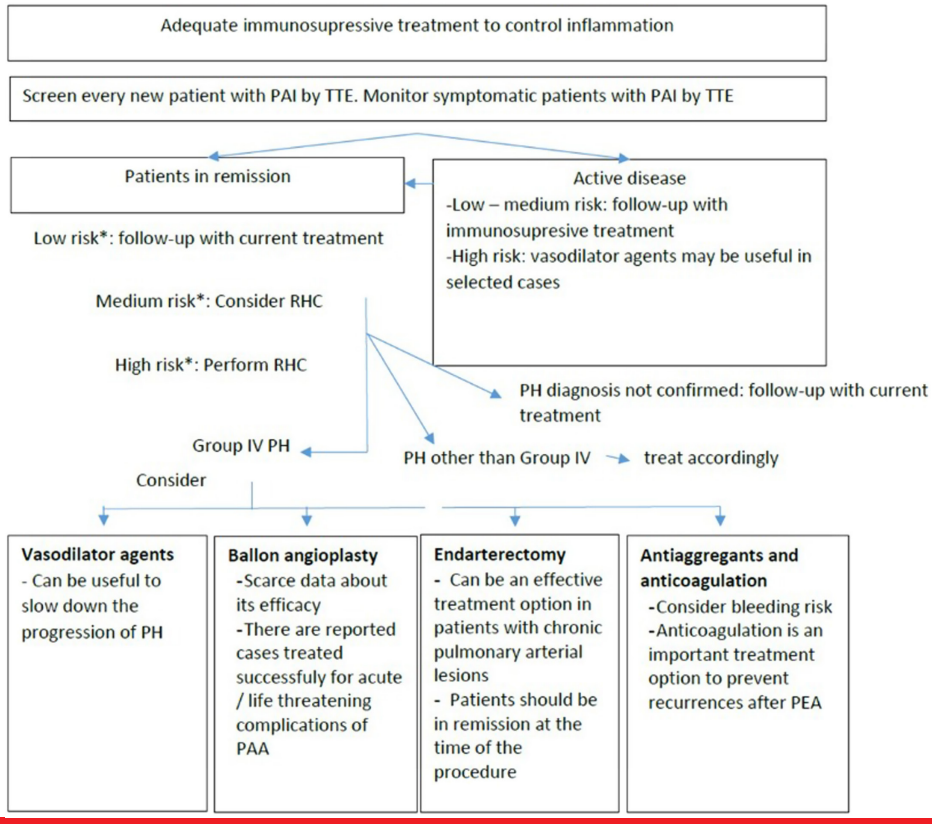

Figure 4. Treatment algorithm for patients with Behçet's disease and group IV Pulmonary hypertension. *According to 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. PAI, pulmonary arterial involvement; TTE, transthoracic echocardiography; RHC, right heart catheterization; PH, pulmonary hypertension; PAA, pulmonary artery aneurysm; PEA, pulmonary endarterectomy.

Moreover, the 3-month follow-up period is too short for the evaluation of immunosuppressive treatment effectiveness in BD with PAI.[43,48] Therefore, PEA should be considered in BD patients with group IV PH who are in remission and who have chronic residual pulmonary arterial occlusive lesions. Lifelong anticoagulation is important after PEA to prevent recurrences.[4] Duration of anticoagulation is another concern in BD because of the risk of bleeding, which has to be defined as recurrences that can occur in patients with PAI.[43-45]

Intravascular interventions (embolotherapy) have been used as effective treatment options in BD patients with PAA.[43,50] There is no data about balloon angioplasty of pulmonary arteries for the treatment of BD with group IV PH. Balloon angioplasty may be effective for the treatment of those with chronic arterial lesions. In addition, a few BD patients were treated with PAH-specific agents that can be used in the treatment of CTEPH.[19,45,48]

SARCOIDOSIS

In sarcoidosis, severe lung parenchymal damage, pulmonary artery compression of hilar lymph nodes, fibrosing mediastinitis, granulomatous angiitis of pulmonary arterioles and venules, pulmonary vasculitis, pulmonary venoocclusive disease or cardiac involvement can lead to PH.[4,5] Although granulomatous angiitis mostly affects medium and small vessels in pulmonary circulation, involvement of large vessels such as the main, lobar, segmental or subsegmental pulmonary arteries can occur in sarcoidosis. The co-existence of TA and sarcoidosis has also been reported. Sarcoidosis-associated vasculitis is responsive to immunosuppressive treatment, although patients may have other conditions that can contribute to the persistence of PH.[15,51]

HOW TO DISCRIMINATE VASCULITIS FROM CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION?

The presence of systemic symptoms or signs should alert clinicians for the diagnosis of primary vasculitis in a patient with a probable diagnosis of CTEPH. The presence of constitutional symptoms, bruits over arteries, decreased pulses in extremities or a history of oral-genital aphthaeous lesions and uveitis are common manifestations of TA and BD, respectively.[15,21,41] Contrast enhancement and concentric thickening of the arterial walls are characteristic features of pulmonary vasculitis detected by CT or MR angiography. Thrombosis of pulmonary arteries, pulmonary infarcts, mosaic attenuation patterns, bronchial arterial dilatation can be observed in both CTEPH and vasculitic syndromes.[16,30] Large pulmonary artery aneurysms are unique for BD; prominent upper lobe pulmonary arterial involvement is common in TA; and enlargement of mediastinal lymph nodes and pulmonary nodules are typical for sarcoidosis.[15,23,25,43] Increased F-18-fluorodeoxyglucose uptake in positron emission tomography can be useful for the differential diagnosis of vasculitis from CTEPH.[16,21,30] Evaluation of systemic arteries that are included in the imaging field can provide additional data for the diagnosis of TA or BD.

FUTURE DIRECTIONS

Most of the current data about group IV PH due to primary systemic vasculitides originate from retrospective or cross-sectional studies or case series. Retrospective data collection and the lack of hemodynamic data were the common limitations in most of the previous studies. Moreover, clinical follow-up data of the patients is not always clear. On the other hand, no randomized controlled trials exist or have been planned for this topic so far. Therefore, in the future, data from carefully planned registries will provide a valuable contribution to patient management.

CONCLUSION

Treatment of group IV PH patients due to vasculitis is challenging. The effectiveness of PAH-specific agents and invasive treatment options with an acceptable complication rate need to be defined in detail. Increasing awareness of this rare but mortal condition among the physicians who are involved in the care of these patients is pivotal. Currently, collaboration of different medical disciplines is crucial to figure out the best treatment option in individual patients.

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