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Insights into etiological factors of pulmonary hypertension in cancer patients

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Pulmonary hypertension is a rare vascular disease that can affect patients with or surviving malignancy resulting in significant morbidity and high mortality. Malignant diseases can lead to elevated pulmonary artery pressure through different mechanisms, either directly by structural obstruction of pulmonary vessels or indirectly through hypercoagulable state or treatment toxicity culminating in high pulmonary vascular resistance. The most common causes of cancer-related pulmonary hypertension are thromboembolic diseases, tumour emboli and treatment toxicity and less commonly intravascular tumours and malignant extrinsic compression.

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Introduction

In recent years, advances in diagnosis and management strategies have improved the long-term survival of cancer patients, and about 60% of patients can now live for five years or more after diagnosis of malignancy [1]. The growing population of cancer-survived patients have a substantial risk of developing cardiovascular diseases due to ageing, co-morbid CV risk factors and cancer-specific adverse effects related to the malignancy itself or treatment toxicity [2]. Cardiovascular diseases have a significant impact on the quality of life and prognosis of cancer-survived patients and are considered the major non-malignant cause of mortality [3–5]. The incidence of CV complications is difficult to estimate precisely due to variability in definitions, the presence of comorbid diseases affecting CV system and data collection stems mainly from registries and case series. The main manifestations of CVD are cardiomyopathy, coronary artery diseases, thromboembolic events, hypertension, arrhythmias, pericardial diseases, valvular heart diseases and vascular diseases [6–8]. Pulmonary hypertension is a rare vascular disease that can affect patients with or surviving malignancy resulting in significant morbidity and high mortality. In this review, we will explore the different etiologies and risk factors of pulmonary hypertension associated with malignant diseases in adult patients.

Pathological insights

Pulmonary hypertension (PH) is defined as an increase in mean pulmonary artery pressure ≥ 25 mm Hg at rest, measured by right heart catheterization. Based on clinical and hemodynamic characteristics, pulmonary hypertension can be classified into five groups including pulmonary arterial hypertension (PAH), pulmonary veno-occlusive disease (PVOD) and drugs and toxins-related (Group1), left heart disease associated

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pulmonary hypertension (Group 2), lung disease associated pulmonary hypertension (Group 3), thromboembolic and vascular obstruction pulmonary hypertension (Group 4) and pulmonary hypertension due to unclear and/or multifactorial mechanisms such as pulmonary tumor thrombotic microangiopathy (Group 5) [9]. Interestingly, pathological studies of primary pulmonary arterial hypertension showed alterations in the cellular regulatory mechanisms controlling the growth and proliferation of pulmonary vascular endothelial cells and smooth muscles with subsequent abnormal proliferation, excessive angiogenesis and resistance to apoptosis which are the hallmarks of malignant diseases pathogenesis [10–12]. Malignant diseases can lead to elevated pulmonary artery pressure through different mechanisms, either directly by structural obstruction of pulmonary vessels or indirectly through hypercoagulable state or treatment toxicity culminating in high pulmonary vascular resistance. The incidence of pulmonary hypertension can be underestimated due to the shared presentation with more common complications in cancer patients such as heart failure and pulmonary diseases. The most common causes of pulmonary hypertension in patients with neoplasia are related to pulmonary vascular narrowing or obstruction (chronic thromboembolic pulmonary hypertension, CTEPH, and tumor emboli) (Group 4) followed by pulmonary arterial hypertension and pulmonary veno--occlusive disease due to treatment toxicity (Group 1) and less common causes include intravascular tumors and malignant extrinsic compression (Group 4).

Thromboemboli

Malignant diseases are a well-known risk factor for venous thromboembolic events (VTE) with 4.1 folds increased risk especially with cancers of pancreas, lung, stomach and primary of unknown origin. Cancer treatment can enhance the risk up to 6.5 folds [13]. Thrombosis in cancer is possibly triggered by the interaction of malignant cells with monocytes or macrophages leading to endothelial dysfunction and activation of platelets and coagulation factors X and XII. Moreover, tissue factor and other procoagulants can be produced by malignant cells. All these prothrombotic factors end with activation of thrombin to produce fibrin binding clot [14]. Thromboemboli can obstruct major pulmonary arteries non-homogenously and persist despite anticoagulation ensuing pulmonary vascular remodelling and ultimate chronic thromboembolic pulmonary hypertension (CTEPH) [15]. The primary cause of CTEPH, in general, is venous thromboembolic events with a history of pulmonary embolism reported in 74.8% of patients and deep venous thrombosis in 56.1%. Malignancy is established as a risk factor for CTEPH with a history of cancer was found in about 12% of patients [16, 17]. A retrospective cohort of 687 patients showed that the odds ratio of CTEPH increased in patients with a history of cancer (OR 3.76, CI 1.47–10.43). Longtime interval to diagnose CTEPH was reported (up to 5–10 years) in survivors of cancer. Tumours of the breast, GIT, melanoma, prostate and seminoma are the most frequently associated with CTEPH [17]. Patients with CTEPH have poor prognosis in the presence of cancer even in patients eligible for surgical treatment with pulmonary endarterectomy [18].

Tumor emboli

Tumor emboli are one type of non-thrombotic pulmonary emboli which separate from the primary tumour mass and reaching the pulmonary vasculature through venous circulation. These emboli are not a part of metastasis process as they remain intraluminal with no invasion of vascular wall tissue. Tumor emboli were found in 2.4–26% of autopsies of solid malignancy patients [19]. The size of the emboli is varying from small (microscopic), which is the most common and associated mainly with cancers of the stomach, liver, pancreas and choriocarcinoma; to the infrequent large (macroscopic) emboli that reported with liver, breast and renal cancers [20]. Clinical consequences depend on the extent of pulmonary vascular bed affected by a persistent mechanical obstruction and secondary reaction to the non--resolving emboli. Patients either remain asymptomatic especially with microscopic emboli or develop subacute dyspnea, cyanosis and features of right ventricular overload due to raised pulmonary artery pressure [21]. The differential diagnosis of pulmonary hypertension in patients with malignancy must include tumour emboli as a potential aetiology since the clinical spectrum are identical to the most common thrombotic emboli. However, identification of tumour emboli is challenging, and diagnosis is probably made post-mortem since imaging modalities are unable to specifically differentiate these emboli from other causes of pulmonary hypertension. Prognosis is poor and no specific treatment apart from palliative measures and management of a primary tumour [20, 22].

Pulmonary tumour thrombotic microangiopathy

Pulmonary Tumour Thrombotic Microangiopathy (PTTM) is a particular presentation of microscopic tumour emboli that triggered diffuse reaction to the deposition of migrating malignant cells by inducing fibrocellular and fibromuscular proliferation in the walls of small pulmonary arteries and arterioles with the formation of microthrombi leading to diffuse vascular obliterations with subsequent pulmonary hypertension [23]. PTTM is rare with an incidence rate 1.4–3.3% in autopsy series and most cases (> 90%) associated with adenocarcinoma, most frequently gastric adenocarcinoma and less commonly lung, oesophagus, liver, colon, common bile duct, pancreas, breast, urinary bladder, prostate and parotid gland carcinomas [24, 25]. It is commonly detected in advanced stages of cancer and can affect patients in younger age (< 40 years). It is possible

for patients to present with clinical features of PTTM prior to the discovery of underlying malignancy. Patients are usually presented with dyspnea and cough progressing to pulmonary hypertension, and right heart failure with rapid deterioration and fatal outcome are the common consequence [26]. Most cases are discovered at biopsy since there are no radiological features specific to PTTM, CT scan may be normal or shows dilated pulmonary arteries, wedge-shaped opacities peripherally, thickened interlobular septa or Tree-in-bud sign (centrilobular nodules with linear opacities) [27]. Perfusion studies may demonstrate defects and pathological studies with cytology and biopsy percutaneously or surgically may help in some cases [28]. Apart from supportive treatment and chemotherapy for the underlying malignancy, no specific treatments are available to withhold this fatal complication with most patients are dying shortly after diagnosis [29]. It is important to consider PTTM as a cause of unexplained dyspnea with malignancy and on the other side to look for undiagnosed cancer in patients presenting with pulmonary hypertension possibly due to PTTM.

Pulmonary artery sarcoma

A rare type of an intravascular tumour originating from the intimal cells of the pulmonary artery with different histopathological types such as undifferentiated, leiomyosarcoma, spindle cell sarcoma and rhabdomyosarcoma [30]. Involvement of pulmonary artery is usually bilateral but can be unilateral. Patients often present with clinical and radiological features mimicking pulmonary thromboembolic disease. Misdiagnosis of pulmonary artery sarcoma for pulmonary chronic thromboembolic hypertension is possible with delayed diagnosis resulting in increased mortality [31]. The prognosis is poor, but overall survival can improve with complete surgical resection with a potential role for post-surgical chemo and radiotherapy. However, curative surgery is not possible in all patients, and symptomatic benefit can be obtained with other surgical options including pulmonary artery endarterectomy [32].

Malignant compression of pulmonary artery

Extrinsic compression of pulmonary arteries by a malignant mass can result in acquired pulmonary artery stenosis with clinical features of pulmonary hypertension and right heart pressure overload. Malignant pulmonary artery stenosis is caused by primary or secondary thoracic cancers especially lung cancer, lymphoma, mediastinal tumours and secondary metastases. Malignant compression can involve one or both major pulmonary arteries. The incidence is not common with few reported cases with a history of malignancy, but it is possible to be the first presentation of cancer. In addition to treatment of underlying malignancy, palliative endovascular stenting can help in promoting symptomatic improvement through relief of pulmonary artery stenosis [33–36].

Treatment-related toxicity

Cardiovascular toxicity is a major complication of specific cancer treatments affecting the quality of life and prognosis. Cardiovascular risk factors, genetic and environmental elements and concomitant use of therapies with negative impact on the CV system can augment the risk of toxicity related to cancer treatment [37]. The damage can be permanent related to cell loss (irreversible damage) or temporary caused by alterations in cellular proteins and mitochondrial structure (reversible dysfunction) [38]. Pulmonary hypertension is a rare but serious side effect of chemotherapy, and it is known to be associated with certain chemotherapeutic agents including dasatinib, cyclophosphamide, bortezomib, carfilzomib and interferon-α [39]. Attention is increasingly focused on the prevention, early detection and treatment of CV complications in patients with malignancy. Recent recommendations from the European society of cardiology emphasized the importance of monitoring patients receiving drugs known for risk of inducing pulmonary hypertension. The surveillance aims for early detection by using clinical assessment and echocardiography before starting treatment as a baseline and at regular intervals thereafter [40].

Dasatinib

A potent tyrosine kinase inhibitor used in the treatment of chronic myelogenous leukaemia by blocking BCR/ABL kinase 1 and in addition inhibiting the SRC family kinases, c-Kit and platelet-derived growth factor-receptor (PDGFR). Dasatinib is associated with a range of significant non-haematological side effects including pleural and pericardial effusion and arrhythmias. Pulmonary artery hypertension is reported in patients using dasatinib but not with other TKI excluding the class-effect possibility. However, the underlying pathophysiological mechanism is unknown, and some suggest a secondary immune reaction or possibly uncontrolled proliferation of vascular endothelium and smooth muscles caused by inhibition of the regulatory SCR kinase [41]. The incidence of PH in patients receiving dasatinib varied from (0.45% to 12%) [42–44] and it can be detected early up to 2 months or late about 48 months after initiation of dasatinib [42, 43]. Follow-up of patients showed reversibility of PH with discontinuation or reducing the dose of dasatinib. However, complete recovery may not be possible in every affected patient after all [44].

Alkylating agents

Development of PVO disease which is an uncommon cause of PH has been reported in 37 patients with different solid organ and haematological malignancies. Prior use of alkylating agents has been identified as the main risk factor

in 83.8% of patients. The implicated alkylating agents with later development of PVO disease are cyclophosphamide which is the most common (43.2%), mitomycin (24.3%) and cisplatin (21.6%). A study of animal models demonstrated a direct relationship between exposure to alkylating agents especially cyclophosphamide and development of pulmonary venous remodelling leading to PVOD and PH. The study also showed a beneficial role for the cytoprotective agents mesna and amifostine to protect pulmonary vasculature from the harmful effects of chemotherapy [45].

In the French registry, patients with squamous anal cancer receiving mitomycin had a higher incidence of PVOD than in the general population with rapid progression and poor outcomes. An experimental study on rats confirmed the role of mitomycin in inducing vascular changes identical to that of PVOD in humans. The study also showed a protective role for amifostine that helped in improving outcomes [46].

Proteasome inhibitors

The ubiquitin-proteasome pathway maintains cellular integrity through degradation of proteins involved in a wide range of processes such as apoptosis, DNA repair and antigen presentation. Dysfunctions in the ubiquitin-proteasome pathway can lead to unbalanced protein synthesis and development of various diseases including malignant diseases [47]. Bortezomib, the first generation of proteasome inhibitors used for the treatment of multiple myeloma and mantle cell lymphoma, has an infrequent incidence of cardiovascular side effects with PH rarely reported [48, 49]. The manufacturer advises stopping bortezomib temporarily in case of diagnosing PH and referring patients for specialist advice. On the contrary, research on animals showed a potential benefit of bortezomib in reversing vascular smooth muscle proliferation and endothelial dysfunction in patients with PAH [50, 51].

Carfilzomib, second generation and more potent proteasome inhibitor effectively used in the treatment of relapsing and refractory multiple myeloma, has been associated with significant cardiac and vascular toxicities including pulmonary hypertension. Phase II studies reported an incidence reaching 2% of PH in patients receiving carfilzomib [52]. The underlying mechanism for vascular adverse effects is not defined yet but could be related to endothelial injury causing impaired vascular relaxation and vasospasm [53]. Reports indicate that PH occurred infrequently especially in patients having cardiovascular risk factors such as atrial fibrillation and arterial hypertension or patients with history of cardiovascular diseases which necessitate close clinical monitoring of those patients in case they develop dyspnea or other signs and symptoms suggestive of PH [54, 55]. Pulmonary hypertension usually occurs early in the course of carfilzomib treatment and it is reversible with discontinuation of treatment and supportive treatment [53].

Interferon α

An immunoregulatory cytokine with antineoplastic features used in the treatment of chronic myeloid leukaemia, hairy cell leukaemia, lymphoma, renal cell cancer, melanoma and Kaposi sarcoma [56]. Interferon α has been reported for a rare but significant risk of pulmonary hypertension [57]. Interferon has been linked to an increased level of Endothelin-1 which is an important modulator in the pathogenesis of PH [58]. Pulmonary hypertension diagnosis may be delayed long, up to 3 years, after initiation of interferon treatment. Discontinuation of interferon is helpful to halt the progression of PH, but in some patients, use of vasodilator therapies was needed [59].

Bleomycin

A cytotoxic antibiotic used mainly in the treatment of Hodgkin lymphoma and germ-cell tumours. Bleomycin is well known for pulmonary toxicity mainly presents as interstitial pneumonitis that can progress to pulmonary fibrosis leading to a high mortality rate 3% [60]. The mechanism of pulmonary toxicity is thought to be related to sever inflammatory reaction releasing cytokines and free radicals leading to endothelial injury and subsequent fibrosis [61]. Pulmonary hypertension rarely develops in patients receiving bleomycin with histological evidence of capillary endothelial oedema and pulmonary veno-occlusive disease has been demonstrated [62]. Bleomycin has been suggested as the main factor in causing pulmonary veno-occlusive disease in a reported series of patients [63, 64]. Bleomycin has long track of being used in experimental studies to induce idiopathic pulmonary fibrosis and pulmonary hypertension [65–68]. Management usually directed toward supportive treatment, steroids and azathioprine with a possible role for imatinib and bosentan [69–71].

Gemcitabine

A cytosine arabinoside analogue used for the treatment of different solid organ tumours either as a single agent for metastatic pancreatic cancer or in combination with other agents for the treatment of lung, breast, and bladder cancers. Gemcitabine is known for myelosuppression and pulmonary side effects but two cases reported for the development of PH after receiving gemcitabine. Clinical and radiological features indicated PVOD as the cause of patients' symptoms that developed secondary to gemcitabine exposure. It is possible that discontinuation of gemcitabine may help in reversing the progression of PVOD and stabilization affected patients [72, 73].

Radiotherapy

There is an increased incidence of cardiovascular complications in patients who received radiotherapy, mainly those with Hodgkin's lymphoma, breast cancer and lung

cancer. However, with advances in radiotherapy protocols and technology, the incidence has been dropped significantly. Pulmonary hypertension is a rare complication of radiotherapy. Pulmonary hypertension has been suggested to be secondary to inflammatory vascular injury provoked by chest radiotherapy leading to arterial remodelling and lumen obliteration [74] that could be similar to vasculopathy triggered by head and neck irradiation that evolve into stenosis of major supra-aortic arteries [75]. Mediastinal fibrosis also implicated as a possible cause of external compression of pulmonary arteries [76]. Sporadic cases of pulmonary artery stenosis have been reported several years after receiving radiotherapy presenting with dyspnea and features of raised pulmonary pressure similar to other more common presentations such as chronic thromboembolic disease [76–78]. Pulmonary artery stenosis needs to be considered in the differential diagnosis of patients with a history of irradiation and dyspnea as the management can be successful with rapid improvement of pulmonary artery pressure using endovascular stenting therapy [77]. Radiotherapy was rarely pointed as a possible cause of pulmonary veno-occlusive disease leading to pulmonary hypertension [79].

Hemopoietic stem cell transplantation

Pulmonary hypertension is one of dreadful complications that can arise following HSCT both in adult and pediatric populations. Although the incidence is rare but it is associated with a considerable morbidity and high mortality (up to 55% of affected patients). Both pulmonary arterial and venous circulations can be involved and patients usually presented early in the first year after transplantation [80]. The underlying mechanism is not clearly defined but the evidence from pathological studies showed an inflammatory process resulting in intimal thickening and vascular wall hypertrophy ending with lumen narrowing and raised vascular resistance [81]. However, it is possible that pre-transplant chemotherapeutic regimes and radiotherapy may have a contributing role in pulmonary vascular damage [82]. Most reported patients have pulmonary arterial hypertension, about 70% of transplanted patients with pulmonary hypertension, mainly involving the arteriolar tree [80]. Pulmonary veno-occlusive disease is a less common cause of pulmonary hypertension after HSCT with endothelial injury, intimal fibrosis and lumen obliteration of venules and small veins result in post-capillary hypertension [83]. Clinical presentation is non-specific similar to other causes of PH and diagnosis can be difficult with lung biopsy may be needed to prove the diagnosis [84].

Conclusion

Cardiovascular diseases are the main health challenge in patients with or surviving malignancy. Although pulmonary hypertension is rare, it carries significant morbidity and mortality and needs to be considered in the differential diagnosis of unexplained cardiopulmonary symptoms. Also, monitoring is necessary for patients receiving treatment with the known risk of pulmonary hypertension.

Conflicts of interest: none declared

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