Pulmonary embolism: A warning sign of occult malignancy

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Thromboembolism (TE) is the leading cause of death among cancer complications. The occurrence rate of TE is different from cancer histology, which most commonly happens in adenocarcinoma. Deep vein thrombosis (DVT) and pulmonary embolism (PE) used to be involved in venous thromboembolism (VTE). In a prospective observational trial of PE, it is diagnosed in up to 5% of patients with cancer on routine imaging scans. The most common cancer types in this study are colorectal (21%) and lung cancer (15%).[1] From another cancer registration survey, the cumulative incidence of VTE in cancer patients ranges from 1% to 8%.[2] While most VTE events are categorized into DVT and PE, there is still a small portion of arterial thromboembolism related to cancer.[3–5] In PE, most proximal PE is regarded as with VTE-like features but segmental PE in the distal branches may be more similar to arterial thromboembolism and correlated with cancer progression. Kraaijpoel et al.[1] showed that patients with segmental PE seemed to have a similar risk of recurrent TE comparable to that of patients with more proximal or multiple clots. Another meta-analysis of PE in lung cancer patients showed that history of COPD, adenocarcinoma, advanced TNM stage (III–IV), chemotherapy history, as well as high levels of serum carcinoembryonic antigen are predisposing factors. The presence of PE in these patients was also associated with poor prognosis.[6]

The etiology of cancer-associated TE has been studied for decades and several molecular mechanisms have been established. Podoplanin is expressed on the surface of many cancer cells and interacts with a platelet activation receptor, C-type lectin-like receptor 2, to induce hematogenous cancer metastasis and cancer-associated TE.[3] Podoplanin sometimes is overexpressed in vascular endothelial cells, which may be induced by thromboinflammation and also contributes to cancer-associated TE.[7] Inflammatory cytokines including IL-1b, TNF-a, or transforming growth factor (TGF)-b1 from cancer-associated fibroblast and cancer cell itself also induced podoplanin expression.[8] Tissue factor (TF), which is overexpressed in several types of cancer and secreted in extracellular vesicles (EV), account for cancer related TE and prognosis.[9,10] TF can activate extrinsic pathway of coagulation cascade and induce thrombin accumulation, finally to TE formation. Vascular endothelial cells may express IL-8 and come into procoagulant status, which is stimulated by cancer released EV with TF. Most human studies with adenocarcinoma showed more TF expression than nonadenocarcinoma tumors, especially in pancreatic cancer.[11] In addition, cancer cells can also secrete adenosine 59-diphosphate to directly activate platelets.[3] In adenocarcinomas, pathologically secreted glycosylated mucins bind to selectins and then interact with L-selectin of leukocyte and P-selectin of platelet, which results in the activation and aggregation of platelets.[3] Even though the above etiologies were discovered, there is still unclear mechanism which may induce distal hypercoagulant status and cause systemically multiple DVT or PE. For example, there is a relatively low risk of distal VTE in head and neck squamous cell carcinoma (HNSCC), though the immunofluorescence studies showed both highly expressed TF and podoplanin in HNSCC tumor tissues and in vitro study also revealed HNSCC cells could produce EV with TF to induce TE.[12] The existence of hypercoagulant factors in microenvironment of HNSCC that only causes local TE but not systemic dissemination, which is similar to the scarcity of distant metastasis in HNSCC, raise a notice of undiscovered mechanism to explain this clinically biological ambivalence.[12]

Alternative approaches for cancer-related TE are to evaluate the patients who were diagnosed as VTE first and then analyze the correlation with cancer occurrence. Baron et al.[13] used Swedish nationwide cancer registry to measure increased cancer risk at least 5 years after VTE diagnosis, and they found especially high risk in first-year follow-up and persistent increased cancer diagnosis as long as 10 years. Carrier et al. conducted a randomized trial to evaluate the newly diagnosed VTE patients with or without computed tomography (CT) imaging for occult cancer detection. Generally, 3.9% of total population was diagnosed with cancer during initial screening or 1-year follow-up. It is noticeable that even with adding CT for screening, 26% of cancer diagnosis was missed, which means there may be a subtle tumor at the time point of cancer-related TE development.[14] In the current study, Lin et al. evaluated 121 newly diagnosed PE in a single institute and originally divided the patients into cancer group (44/36%) and non-cancer group (77/64%). Baseline characteristics were similar except there was higher body mass index, hyperlipidemia, and coronary artery disease in non-cancer group. After 1-year follow-up, high incidence of cancer diagnosis (6/59, 10.17%) from non-cancer group was reported.[15] Although the case number is small, higher occult malignancy rate comparing

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with previous studies is noticed. The ethnic difference may be explained for the high malignancy rate in this study since non-cancer-related risk factors for VTE are relatively low in Taiwanese and those patients diagnosed with PE may be more likely due to cancer-related TE with occult malignancy. It is therefore interesting to know the cancer types for these patients with PE in this study, which may be correlated with the final prognosis, too.

Cancer patients have high incidence rate of PE, which sometimes is fatal, and vice versa. Early detection of occult malignancy in newly diagnosed PE is still challenging and the mechanism of cancer-related TE formation from occult malignancy is still unclear. In the future, more data collection from different cancer types correlated with specific TE patterns, such as multiple VTE or segmental PE, may be helpful for novel biomarkers identification. New treatment policies which can target cancer-related TE may also have the potential to target cancer metastases, since there has been a close relationship between these two unresolved issues.

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