Peer Review File

Article Information: Available at http://dx.doi.org/10.21037/amj-20-114

Comment 1: Please highlight the unique of this case in Abstract regarding checklist 3a. The Unique emphasis should be on the diagnosis of pancreatic cancer with pulmonary tuberculosis and venous thromboembolism.

Reply 1: We added some text to emphasis on the unique of this case as pulmonary tuberculosis with venous thromboembolism as rare presentation in pancreatic cancer (see page 4, line 101-108).

Changes in the text:

To our best knowledge there have been no reported cases of pulmonary tuberculosis with venous thromboembolism as the initial presentation of pancreatic cancer. The exact pathogenesis regarding venous thromboembolism with tuberculosis in pancreatic cancer is still unknown and debatable. Herein, we report an interesting case of smear positive pulmonary tuberculosis (PTB) with venous thromboembolism leading to the elusive diagnosis of advanced pancreatic cancer. We discuss on possible novel hypotheses for the mechanism of venous thromboembolism in pancreatic cancer as well as association between tuberculosis and pancreatic cancer.

Comment 2: Please provide information regarding checklist 5c.

Reply 2: We have added medical, family, and psycho-social history including relevant genetic information (see page 5, line 133-137)

Changes in text:

The past medical history included diabetes mellitus and ischemic heart disease. He had no history of smoking and did not drink alcohol. He was a retired general practitioner in a local clinic. His medications prior to the diagnosis included Mixtard insulin injection, bisoprolol and aspirin. There was no family history of malignancy, tuberculosis or hypercoagulable disorder.

Comment 3: A timeline figure is suggested regarding checklist 7.

Reply 3: We added a timeline figure as advised (see page 13, figure 3)

Changes in text:

The event	**Timeline**
Diagnosis of smear positive pulmonary tuberculosis.	January 2019
First presentation for deep vein thrombosis and pulmonary embolism.	February 2019

Patient deteriorated even on standard treatment for venous thromboembolism and tuberculosis.	March 2019
Investigations for malignancy (CT scan and serum tumour marker) and diagnosis of pancreatic cancer.	April 2019
Palliative care for pancreatic cancer and end of life.	May 2019

Comment 4: Figure 2(b)should be modified to "Tail of pancreas is atrophy with dilatation of pancreatic duct (arrow)". Please check to avoid other typos

Reply 4: we have modified the text as advised (see page 12, figure 2(b))

Changes in text: Tail of pancreas is atrophy with dilatation of pancreatic duct (arrow)

Comment 5: In recent years, there are many studies have discussed pancreatic cancer and venous thromboembolism. Please discuss the possible mechanisms in depth. In the possible mechanisms, is there a possible link between pulmonary tuberculosis, venous thromboembolism and pancreatic cancer?

Reply 5: We did more reviews on the recent studies regarding pancreatic cancer with venous thromboembolism, tuberculosis with thromboembolism as well as tuberculosis in pancreatic cancer. We have done a summary as the below text. However, to our best knowledge, there was no study in link between tuberculosis, venous thromboembolism and pancreatic cancer. In addition, we cited more literatures as per our references. (see page 6 and 7, line 177-236; for references see page 9 and 10, line 292-370)

Changes in text:

A number of studies looking for occult malignancy in patients with idiopathic deep vein thrombosis place pancreatic cancer among the most common causes found (2). Several recent studies have shown that the incidence of venous thromboembolism is highest in patients presenting with metastatic cancer, particularly pancreatic cancer and carry poorer prognosis (3).

Armand Trousseau first reported on the relationship between thrombosis and cancer in 1865. Thrombotic complications in cancer can vary from arterial or venous thromboembolism to disseminated intravascular coagulation (4,5). It has long been recognised that pancreatic cancer has a peculiar and unique ability to induce a hypercoagulable state that may lead to clinically apparent thrombosis. A number of risk factors for venous and arterial thrombosis have been identified in cancer patients. These include certain comorbidities, surgery, immobility, tumour histology and stage, the presence of indwelling central venous catheters, and chemotherapy and/or some

molecular targeted therapies (6). Despite the well-known association between cancer and thromboembolic disease, the mechanisms that promote thromboembolic events in cancer patients are not clear and appear to be multifaceted (7). However, in the last decade, new insights into the biological mechanisms responsible for hypercoagulability in pancreatic cancer have been reported, potentially uncover novel therapeutic options (8,9).

Pancreatic cancer is characterised by the peculiarity of a high level of expression of tissue factor in tumour tissue and the release of tumour-derived microvesicles that might promote distal thrombosis by activating both the extrinsic and intrinsic pathways, as well as by promoting platelet adhesion and activation, and the release of neutrophil extracellular traps from leukocytes (10,11). Furthermore, other coagulation pathways probably contribute to these processes, such as those that involve heparinase (12), podoplanin (13,14) and hypofibrinolysis. Plasminogen activator inhibitor-1 as a potent inhibitor of fibrinolysis which can be released by pancreatic tumour cells and activated platelets (15,16). Importantly, pancreatic cancer has to be considered a dynamic milieu of cellular and acellular elements including fibroinflammatory stroma, extracellular matrix and infiltrating immune cells, in addition to the cancer cell population. Thus, postulating that pancreatic cancer induced hypercoagulability is the result of procoagulant properties of cancer cells themselves together with the procoagulant properties of elements present in the microenvironment (17).

Venous thromboembolic events in tuberculosis is a rare occurrence, but few cases have been reported in literature (18). All the three components of Virchow's triad, i.e., hypercoagulability, venous stasis, and endothelial dysfunction, can play a role in the pathogenesis of the venous thromboembolism associated with tuberculosis. There are several mechanisms in tuberculosis that can produce a hypercoagulable state to promote thromboembolic complications. There are several studies that have shown increased level of plasma fibrinogen, impaired fibrinolysis along with reduction in antithrombin III, protein C, and reactive thrombocytosis resulting in a hypercoagulable state in which venous thromboembolism can occur in pulmonary tuberculosis. (19,20). However, clinical deterioration with the thrombosis in tuberculosis patient despite proper management alarmed us for the extensive workup of malignancy.

Although tuberculosis and cancer are very common diseases, there has been little attention to the pathophysiological and practical implications of their co-existence. The association between tuberculosis and cancer has rarely been reported. Of note, malignancies and the instituted therapies for their management seem to create the proper environment for either the reactivation of a latent tuberculosis infection or, more rarely, for the acquisition of a primary mycobacterial infection. Immunosuppression, especially depression of the T-cell defense mechanisms, is associated with mycobacterial infections (21). In short, there is paucity of study and analysis regarding the mechanism of tuberculosis in pancreatic cancer. Its association with tuberculosis is a rare occurrence, and very few cases have been reported in literature. To our best knowledge, there was no previous review for the possible link between venous thromboembolism, tuberculosis and pancreatic cancer. Nevertheless, pancreatic cancer has a complex molecular landscape with high potential for future discovery.