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Mini Review

Porto-Splenic Thrombosis-An Intriguing Complication of Tuberculosis

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Abstract

Tuberculosis is one of the most common infectious diseases in developing countries. Rather than a localized disease it is now considered as a cause of systemic inflammation. Thrombovascular complications secondary to tuberculosis are now increasingly been reported. Porto splenic thrombosis is one such rare category which sometimes presents as an atypical manifestation of tuberculosis. In this article we reviewed various case reports of Porto splenic thrombosis and discuss about the mechanism behind it.

Keywords: *Porto Splenic Thrombosis; Tuberculosis (TB)*

Introduction

Tuberculosis (TB) has been a nightmare for the human civilizations for almost centuries. Discovery of tubercle bacilli by Sir Robert Koch in 1882, kick started the research in the pathogenesis of tuberculosis. Initially thought to be a disease of lung parenchyma, it was later known to affect virtually every system in human body. It may present as a focal granulomatous lesion or in disseminated form presenting as pyrexia of unknown origin. The patients are mainly classified as pulmonary or extra pulmonary disease. Constitutional symptoms such as fever, weight loss, anorexia and night sweats are often seen in all the forms of Tuberculosis. Apart from that patient can have systemic or organ specific symptoms such as neurologic impairment in CNS tuberculosis, malabsorption, intestinal obstruction or ascites in abdominal tuberculosis, cough, expectoration, chest pain and dyspnea in pulmonary and pleural forms respectively. It may also have atypical presentations such as infertility, joint involvements mimicking septic arthritis and spinal cord compression, hepatic abscess and vascular involvement in form of venous thrombosis.

Despite the availability and acceptability of highly effective anti-tubercular therapy tuberculosis is still considered a deadly disease and is a menace especially in the developing countries. In the era of modern medicine, dilemmas still persist about the unusual presentations and associations of tuberculosis. Most of these are mainly due to the systemic inflammation caused by the disease that is present at any focus in body and not necessarily imply disseminated disease [1]. The implicated inflammation has a major impact on vascular system and can present as vascular thrombosis at different sites. Medenox study evaluated various risk factors for venous thromboembolism (VTE) in acutely ill hospitalized general medical patients and found cute infectious disease as an independent risk factor with an odds ratio of 1.74 [2]. In a multivariate analysis model, active tuberculosis had a risk of VTE close to the risk associated with neoplasia [3]. Vascular

thrombosis in tuberculosis has been reported previously in last few decades. The most common site was deep veins in lower limbs. Reasons for this may be multifactorial such as more prominent symptoms, easy accessibility of venous system for diagnosis and anatomic factors. Deep venous thrombosis has been associated with 1.5% - 3.4% cases of TB [4]. Rare case reports also suggested cerebral venous thrombosis, retinal vein occlusion, aortic and vena caval thrombosis [5-8]. Portosplenic venous thrombosis is one such rare complication of tuberculosis which has been reported in the recent decades. Site affected varied from hepatic IVC to splenic or portal vein. Symptoms varied vastly from non-specific pain abdomen to ascites, upper gastrointestinal bleed and Budd-chiari syndrome. Mostly the cases were associated with abdominal tubercular lymphadenopathy but not as a rule. Some were diagnosed with disseminated or pleuropulmonary TB.

We studied various case reports of thrombosis in hepatosplenic axis that were secondary to tuberculosis. Table 1 shows summary of various case reports.

Authors	No. of patients	Site of thrombosis/ compression	Site of tuberculosis	Year of publication
Kourilsky R., *et al*. [9]	1	Compression of hepatic pedicle	Tuberculous lymphadenopathy	1961
Tete R., *et al*. [10	1	Splenic vein	Tuberculous lymphadenopathy	1970
Ruttenberg S., *et al*. [11]	2	1. Splenic vein thrombosis 2. Portal vein thrombosis	1. Tubercular lymphadenopathy 2. TB pancreas	1991
Caroli Bose FX., *et al*. [12]	1	Portal vein thrombosis	Hepatic hilar lymphadenopathy	1997
Gogna A., *et al*. [13]	1	Hepatic IVC	Pleuropulmonary TB	2004
Venkatesh SK., *et al*. [14]	1	Portal vein	Hepatic TB	2005
Bhalla AS., *et al*. [15]	7	Case series 2002 - 2010 Splenoportal thrombosis	Abdominal tuberculosis lymphadenopathy	2010
Ozseker B., *et al*. [16]	1	Portal vein thrombosis	Abdominal tuberculosis with ascites	2012
Dan X., *et al*. [17]	1	Portal vein	Hepatic hilar LAP	2014
Jain D., *et al*. [18]	1	Splenic vein thrombosis	disseminated	2014
Wariyapperuma UM., *et al*. [19]	1	Portal vein	Peritoneal TB	2015

Table 1

Discussion

Tuberculosis is still one of the most prevalent infections in developing countries like India. And it is frequently associated with other co-morbidities such as diabetes, cardiopulmonary disorders and other infections such as HIV. In all these scenarios, symptoms of tuberculosis itself may be masked by the other organ dysfunction and patient may be detected with atypical finding such as vascular thrombosis. Portosplenic axis thrombosis is one of such rare presentation. Portal hypertension has traditionally been seen secondary to chronic liver disease or due to extrahepatic portal venous obstruction (EHPVO). Most common cause of portal vein thrombosis is malignancies, liver cirrhosis and thrombophilia which may be acquired or inherited. Tuberculosis stands as a systemic disease which can mimic a thrombophilic disease due its impact on hemostatic factors [20]. So knowledge about this complication is very important for overall management and to save the patient from resulting irreversible sequelae.

Virchows triad dictates that thrombosis is a result of vascular stasis, endothelial injury and hypercoagubility. Tuberculosis in its different forms has contribution in all the three components of the triad.

Endothelial injury

It is a well-known fact that inflammation induces endothelial dysfunction which in turn leads to a prothrombotic state [21]. Various experimental studies done on pathogenesis of TB have proven that the disease is associated with a significant increase in pro-inflammatory markers such as TNF-alpha, IL-6, IL-1 and fall in anti- inflammatory IL-10 [22]. Most of the inflammatory markers are released from macrophages after ingesting the mycobacteria to activate T-cell response. Studies had shown that there is an increase in tissue factor expression which could be a major implicator in intravascular thrombosis *in vitro* [23]. Hwang., *et al.* studied the role of mycobacterial cell wall glycolipid trehalose 6,6'-dimycolate (TDM) in inducing inflammation and granuloma formation. Similar model was also implicated in inducing pathological hyper coagulation. The observed vascular occlusion indicated that obstruction was likely due to subendothelial localized activity leading to restriction of blood vessel lumens [24].

Hypercoagubility

Active TB has been associated with an alteration in coagulation factor levels such as elevation in plasma fibrinogen, factor VIII, plasminogen activator inhibitor I with depressed antithrombin III and protein C levels [9]. Protein C is a natural anticoagulant that functions through selective inactivation of Factors Va and VIIIa. Decrease in level of this protein results in increased unprovoked thrombosis [25]. Increase in coagulation factors in tuberculosis represents the cross talk between inflammation and coagulation pathway [26]. Tissue factor is the first common link and trigger between both the pathways to initiate host response to invading pathogen. This is followed by downstream molecules such as thrombin which mediate the inflammation. Reactive thrombocytosis is also seen as an inflammatory marker in different settings including infectious diseases. In case of tuberculosis it has been linked to increase IL-6 levels and has a prognostic role [27]. In addition, hyper aggregation of platelets has also been documented in patients of tuberculosis [28].

Vascular stasis

Sometimes tubercular lymphadenopathy can become massive and cause compression of nearby structures including vessels. Cases of renovascular hypertension and internal jugular venous thrombosis due to lymph node compression have been reported in case reports [29,30]. Possible association between antitubercular drug rifampicin and thromboembolism has also been postulated, however, the exact mechanism is not known [31]. An observational study by Saluja M., *et al*. reported increased thrombotic events in patients taking rifampicin containing regimens [32]. Intermittent dosing schedule of rifampicin has been associated with development of a type I immunoallergic reaction leading to complement activation and in some cases resulting in disseminated intravascular coagulation (DIC) [33]. This can also be an explanation of the above possible association.

Treatment of thrombosis with tuberculosis deals with two aspects - treating the primary cause and revascularization. Antitubercular therapy (ATT) has been the standard of care for tuberculosis. So, starting ATT seems the reasonable first approach. However, there were cases where thrombus was diagnosed months after starting ATT [14]. Also, the postulated association of thromboembolism with rifampicin further complicates the issue. Still all the patients are given ATT regardless of the site of thrombus and its correlation with site of active focus. Anticoagulation in the form of Low molecular weight heparin initially followed by maintenance with oral vitamin K inhibitors such as warfarin has been used in all the patients. None of case reports suggested thrombectomy as the modality of treatment. When followed patients gradually improved in terms of tuberculosis symptoms and signs, however thrombus dissolution was not documented in most of the cases.

Although most cases of portosplenic thrombosis were associated with abdominal tuberculosis, the mechanism behind is more attributable to systemic inflammation than local factors. Long term follow up is needed to know about the sequelae and impact on portal circulation. What remains unanswered is that which patients are at increased risk as only a small number of patients develop this complication. Also, the question arises that should prophylactic anticoagulation be given to patients who have a prothrombotic genetic mutation and develop tuberculosis.

Conclusion

Tuberculosis is one of the most interesting infections known to mankind by the fact that it can involve any system and can manifest in a number of forms. Thrombosis of porto-splenic circulation is one of the rare presentations. As traditionally this entity is associated with liver cirrhosis and other thrombophilic conditions, one needs to have a high degree of suspicion to diagnose it in a patient of tuberculosis who presents with atypical abdominal symptoms.

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