Case Report

Coexistence of disseminated tuberculosis and peripheral deep vein thrombosis in a child with newly diagnosed celiac disease: A rare entity

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Abstract

Some case reports have been published suggesting association of celiac disease (CD) with tuberculosis (TB) and with deep vein thrombosis (DVT) but mostly in adult populations and in different patients. We report a 13-year-old girl recently diagnosed with CD presented to pediatric emergency at a tertiary teaching hospital in north India with complaints of generalized weakness, pain and swelling over left lower limb that subsequently was diagnosed to have disseminated TB and left lower limb DVT. She was treated with course of anti-tubercular drugs, short-term anticoagulant therapy, and gluten free diet with positive outcomes over next 3 months. To the best of authors' knowledge, no previous reports have yet suggested a coexistence of disseminated TB and peripheral deep vein thrombosis and CD in one single pediatric patient.

Keywords: Association, celiac, child, gluten-free, thrombosis, tuberculosis disease

Introduction

Celiac disease (CD) is a multi-systemic entity which includes malnutrition and is also associated with manifestations like increased risk of malignancy such as lymphoma and other autoimmune diseases, and tuberculosis (TB). Williams was the first to establish a possible association between CD and TB.[1] Individuals with CD also have an evidence of poor vitamin status mostly, low serum vitamin D levels and increased levels of homocysteine among patients following a gluten-free diet. This in turn increases the risk of thromboembolism in CD patients.[2] In literature, some studies have suggesting coexistence of CD with TB and peripheral deep vein thrombosis (DVT) but are mostly limited to adult populations. Very few case reports have been published in the literature suggesting these associations in the pediatric population. Here, we are reporting a case of a child having the rare co-occurrence of disseminated TB and peripheral DVT where the diagnosis of celiac disease was made recently.

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Case Report

A 13-year-old girl child presented with chief complaints of generalized weakness, pain, and swelling over left lower limb for 5 days in pediatrics emergency of tertiary care hospital. The child was diagnosed with CD 1 month back by duodenum biopsy, tissue transglutaminase antibody IgA. On examination, the patient was thin built and emaciated. Her height was 144 cm and weight was 22 kg, vital parameters were stable, and child had pallor, generalized lymphadenopathy in the form of enlarged significant lymph nodes over cervical, axillary, and inguinal region. Left lower limb was swollen and showing dilated and tortuous vein. On systemic examination, there were no significant positive findings. Blood investigation showed following results: hemoglobin (Hb)

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= 7 gram%, total leukocyte counts (TLC) = 4000/cubic mm, differential leukocyte counts (DLC): neutrophils = 80%, lymphocytes = 15%, monocytes = 1%, eosinophils-1%. Blood urea = 27 mg%, serum creatinine = 0.7 mg%, serum uric acid = 3 mg%, serum aspartate aminotransferase (AST) = 157 IU, alanine aminotransferase (ALT) = 160 IU, serum protein = 4.9 gm%, prothrombin time (PT) = 23.7 s, partial thromboplastin time with Kaolin (PTTK) = 69.5, international normalized ratio (INR) = 2.03, serum Vitamin D3 = 12 ng/dl.(>30 ng/dl considered normal). On Doppler examination, an echogenic thrombus was present in left common femoral and left deep femoral vein making a diagnosis of left lower limb deep vein thrombosis. Furthermore, coagulation studies were done showing antithrombin (AT) III = 26% (normal range 17–30%), Protein C = 98.33% (normal range 70–150%), Protein S = 100.52% (normal range 70–150%), Prolactin = 6.35 ng/ml (normal range 2.8–29.2), Homocysteine = 5.63 umol/l (normal range 3.7–13.9), Factor V Leiden mutation < 220 copies/ml essentially a normal study. The patient was started on intravenous antibiotics and appropriate intravenous fluids in view of high grade fever and early signs of septic shock. During the hospital stay, patient continued to have high grade fever, although clinical condition apparently became stable. Work-up for fever came up with chest X-ray having multiple nodular opacities, ultrasonography of abdomen showed multiple enlarged paraaortic, pre-aortic peri-pancreatic, and inguinal lymph nodes. Remaining investigations like CBC was within normal range, Monteux skin test was negative, blood cultures were sterile, and sputum for Acid Fast Bacilli (AFB) was negative. Later on day 7 of admission, patient had an episode of seizure. On being evaluated, Serum Calcium = 7 mg%, ionized calcium = 3.22 mg%, and CSF examination was normal, magnetic resonance imaging (MRI) brain showed multiple granulomas, making presumptive diagnosis of TB or Lymphoma [Image 1]. Contrast Enhanced Computed Tomography (CECT) Chest showed multiple opacities and enlarged hilar, mediastinal lymph nodes suggestive of TB or Lymphoma [Image 2]. Bronchoalveolar lavage (BAL) fluid examination showed occasional 1–2 acid fast bacilli. Further cartridge-based nucleic acid amplification (CBNAAT) was run on BAL fluid which confirmed diagnosis of TB without any drug resistance. Abdomen CECT showed multiple enlarged lymph nodes. CT guided lymph node biopsy was taken suggestive of TB showing Acid Fast Bacilli on Zeil Neilson stain. Bone marrow examination showed tubercular granuloma and iron deficiency anaemia. The final diagnosis of CD with lower limb DVT with disseminated TB was made and the patient was put on anti-tubercular treatment (ATT) along with warfarin and low molecular weight heparin (LMWH, Enoxaparin) was started after 5 days of warfarin overlap in prescribed doses. Enoxaparin was continued for next 3 months. The patient is being regularly followed up in Out Patient Department and has maintained strict compliance with gluten-free diet. After 1 month, the patient was gaining weight, Hb improved to 11 gm%, and Doppler study of leg showed resolving stages of thrombus. The same treatment was continued and after 3 months, thrombus was completely resolved. The anticoagulant was stopped and ATT was continued for next 6 months. Now the patient is on regular follow-up and after 1 year has shown no signs of any residual illness. The ethical permission was obtained from Institutional Ethics Committee and a written informed consent was obtained from parents of the child for publication of this case report.

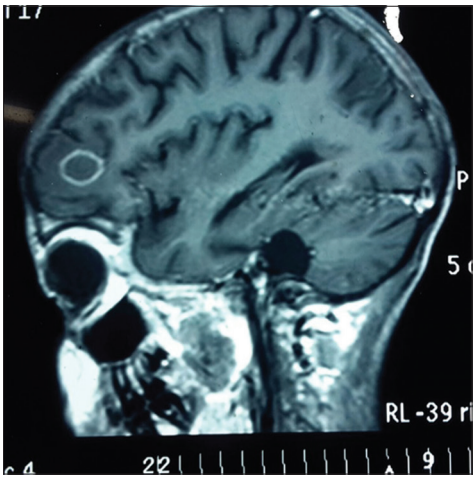

Image 1: Magnetic Resonance Imaging of (MRI) brain of a 13-year-old girl with generalized weakness and seizures on the 7th day of admission showing multiple granulomas in the brain probably of Tuberculoid or lymphoid origin

Discussion

CD and TB account for 9% and 4%, respectively, for malabsorption cases in pediatric population in northern India.[3] In last few decades there is almost 3–4 times increased risk of TB among CD patients.[4] There may be several postulations for the association between CD and TB. One hypothesis is that individuals with CD often have persistent low-grade inflammation which affects the vitamin status, also gluten-free diet is often low in vitamin D, increasing the risk of deficiency of vitamin D and accompanied with malnutrition in children, it increases the risk of TB.[5,6] The pathogenesis is, "Vitamin D has been shown to

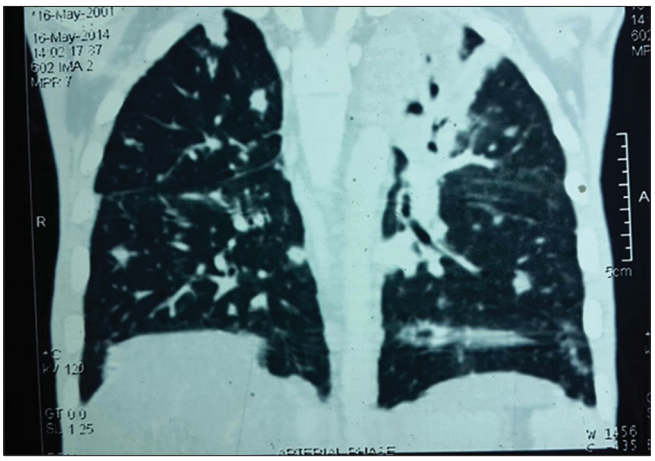

Image 2: A Contrast-Enhanced Computed Tomography (CECT) Thorax 13-year-old girl with suspected Disseminated Tuberculosis showing enlarged multiple lymph nodes probably of Tuberculoid origin

induce the synthesis of nitric oxide in macrophages, thus acting to suppress the growth of Mycobacterium TB in these cells".[7] Thus, suppressed cell-mediated immunity and/or malnutrition increases susceptibility to infection as postulated by William *et al.* as well in their study.[7] Vitamin D augments the effect of IFNγ (Interferon Gamma) in promoting the granulomatous process and thus promotes the differentiation of monocytes into epithelioid cells and multinucleated giant cells".[7] Both of these cells form prominent parts of tubercular granulomas. Many studies have reported Vitamin D deficiency in patients having TB. These studies have also shown an association of genetic variants of the vitamin D receptor and TB infection.[5] Further association of CD with peripheral DVT has been studied by focusing on levels of homocysteine, low levels of folic acid and low vitamin D status.[8] It is also well known that if a patient complies with gluten-free diet this may not always ensure complete recovery of small intestine as "only 8/39 adults on a long-term gluten-free diet had a fully recovered duodenal mucosa."[9] Therefore, inflammation and malnutrition often persist in CD. Hypercoagulable state could have been induced by TB itself as well by several mechanisms like due to deficiency of AT III, Protein C, Protein S, and raised levels of fibrinogen among others.[10] Factor V Leiden, lupus anticoagulant and anti-cardiolipin, homocysteine level, protein C and S levels were negative in the index case. We could not establish the etiology of thrombotic tendency in the index case. In literature as well, exact etiological factor for thrombosis in most of the cases of CD is yet unknown.[11]

Conclusion

Celiac disease is an autoimmune syndrome and is also associated with other disorders as well. In the index case, the patient had CD along with disseminated TB and peripheral DVT. There are many studies which show a correlation between CD and TB but there is limited data showing the association between celiac disease and DVT and that too is restricted to adulthood only. We could not find any case having the combination of these three different entities, that is, CD with peripheral DVT and disseminated TB in a single patient so, this case is being reported as a novelty to add to existing literature. This will help primary care physicians in early diagnosis of rare presentations in pediatric patients and early treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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