First Report of an Association Between Crohn's Disease and Isolated Splenic Tuberculosis in Pediatric Population

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Abstract

Isolated splenic tuberculosis (TB) in children is extremely rare, and congenital or acquired immunodeficiency is usually a predisposing factor for this disease. Herein, we report a case of isolated splenic TB in a 5.5-year-old child associated with Crohn's disease. As far as we are aware, this association is reported for the first time in children. Clinicians should be aware and consider extra pulmonary TB, especially in endemic regions. In addition, evaluation of an underlying disorder in unusual presentations of TB is advisable.

Keywords:
Crohn's disease, Mycobacterium, Pediatrics, Splenic tuberculosis, Tuberculosis

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Introduction

A rising incidence of inflammatory bowel diseases (IBDs) has been observed in both pediatric and adult populations in recent years.[1] Overall,15%-25% of patients with Crohn's disease present in childhood and the incidence of this disease during childhood is between 2.2 to 6.8 per 100 000.[1]

Isolated tuberculosis (TB) of the spleen is also extremely rare, not only in pediatric but also in adult populations.[2] The disease is usually misdiagnosed as splenic abscess (bacterial or fungal), lymphoma, carcinoma of the spleen, and rheumatic disorders.[2]

Herein, we report a 5.5-year-old girl with isolated splenic TB and Crohn's disease.

As far as we are aware, this association is reported for the first time in the pediatric population.

Case Report

A 5.5-year-old girl was admitted to Ali Asghar Children's Hospital with a fever of unknown origin (FUO). She had a fever for 2 weeks before admission, and at the first visit, her physical examination was normal except for axillary temperature at 38°C. The laboratory data revealed white blood cell (WBC) 23500/mm^3 (polymorphonuclear 70%, band 4%, lymphocyte 22%, and mononuclear 4%), hemoglobin 10 g/dL, mean corpuscular volume (MCV) 79 fl, platelet 589 000/mm^3, erythrocyte

sedimentation rate (ESR) 82 mm/h, C-reactive protein (CRP) 121.5 mg/L and ferritin103 ng/mL. Blood and urine culture, Wright, Coombs Wright, Widal test, and tuberculin skin test (TST) were negative. Liver function test (LFT) and serum electrolytes were within normal range. Chest radiography and paranasal sinus (PNS) computed tomography (CT) were normal. On the 7th day of admission, a few bilateral symmetric skin lesions appeared on her legs being compatible with erythema nodosum.

Abdomino-pelvic ultrasound revealed multiple hypoechoic target lesions in the spleen in favor of micro abscess and multiple mesenteric lymph nodes with an upper size of 10 mm without organomegaly. Abdominal CT with contrast confirmed the ultrasound results (Figure 1). Bone marrow aspiration and culture results were unremarkable. The patient underwent an open spleen biopsy (Figure 2) to find the etiology of the hypoechoic lesions with a preoperative diagnosis of probable lymphoma.

The pathologic report was granuloma with caseation necrosis compatible with TB (Figure 3), but QuantiFERON-TB Gold (QFT) and polymerase chain reaction (PCR) evaluation for *Mycobacterium tuberculosis* and atypical mycobacteria on the spleen and bone marrow specimens were negative. However, the patient was treated for TB. Treatment started with rifampin, isoniazid, ethambutol, and pyrazinamide and continued with the two first drugs after 2 months of therapy. The fever subsided within 7 days, and the patient was discharged one week after starting the treatment while she was dramatically in good condition and was followed up monthly. Monthly abdominal ultrasound revealed the disappearance of the splenic lesions in the third month of treatment; at the same time, the patient came back with the complaint of fever recurrence and diarrhea. The results of the laboratory test at the second admission showed positive Clostridium difficile toxin A in the stool examination. So the patient was treated with metronidazole for the primary diagnosis of pseudomembranous colitis, and anti-TB drugs were discontinued not only for this problem but also for serum glutamic pyruvic transaminase (SGPT) result, which was five times upper than the highest normal limit. The patient became afebrile for three days, and the frequency of diarrhea decreased,

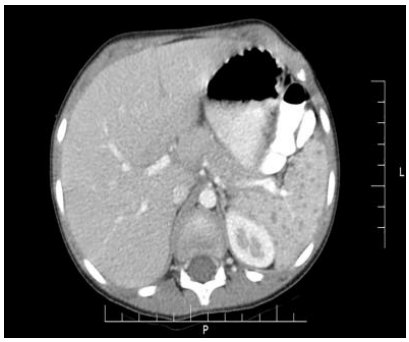

Figure 1. Abdominal CT with contrast reveals multiple microabscesses in the spleen.

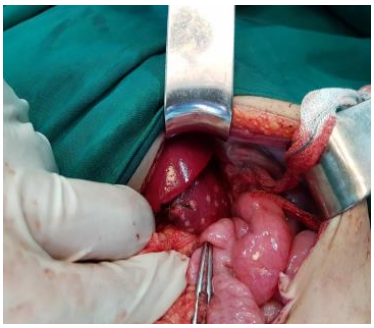

Figure 2. Multiple abscesses are revealed during the exploration of the spleen at open biopsy.

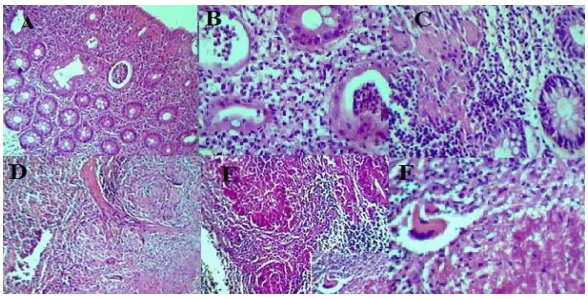

Figure 3. Histological features of colonic Crohn's disease (A-C) and the typical architecture of a TB granuloma (D-F). (A) The superficial aspect of the colon wall shows deep ulceration and prominent submucosal inflammation, including cryptitis and crypt abscess formation (B) Medium power view of cryptitis and crypt abscess extending from the superficial mucosa into the deep mucosa (C) High power view of the deep aspect of the muscularis propria showing an epithelioid granuloma (D) representative of granuloma with central necrosis being adjacent to spleen tissue (E) A well-defined granuloma composed of predominantly histiocytes surrounded by lymphocytes, plasmocytes and Langerhans giant cells with central caseating necrosis (F) Representative of a tuberculoid like granuloma with central necrosis and Langerhans giant cells (Hematoxylin & Eosin × 200).

but the fever and diarrhea relapsed more severely, and erythema nodosum lesions appeared on the upper and lower extremities. The patient was evaluated for recurrence of TB, but the chest radiogram was normal, and abdominopelvic ultrasound revealed no lesion. Some aphthous lesions appeared on the soft palate and buccal membrane of the oral cavity. With a primary impression of inflammatory bowel disease or intestinal TB, the patient underwent colonoscopy and biopsy. The surface of the colon was involved with ulcers, and the final pathologic diagnosis was compatible with Crohn's disease (Figure 3). Regarding the signs and symptoms, endoscopic findings, and the pathologic results of the colon biopsy sample, the final diagnosis of colonic Crohn's disease was established.

According to the Pediatric Crohn's Disease Activity Index (PCDAI),[3] the patient had mild Crohn's disease.

PCR evaluation on the colon specimens for herpes simplex virus, cytomegalovirus, and *M. tuberculosis* complex was negative. The patient was treated with 5-aminosalicylic acid, and the fever and diarrhea dramatically subsided in 48 hours. Anti-TB drugs (rifampin and isoniazid) were re-started 7 days after normalization of LFT.

Evaluation for immune deficiency, including CD markers studies, revealed no abnormal results in humoral and cellular immune systems. Since the first PCR for *M. tuberculosis* was negative despite clinical response to the anti-TB treatment, the spleen specimen was checked again, and the PCR of *M. tuberculosis* became positive on the second examination. We continued the anti-TB regimen for 6 months, and the Crohn's disease is now controlled under treatment and close observation. The 4-year follow-up did not show any recurrence of TB.

Discussion

The spleen might be involved in the course of TB as an isolated involvement or being secondary to miliary TB. Although there are few studies that have reported isolated splenic TB in immunocompetent cases,[4,5] usually, a congenital or acquired immunodeficiency is a predisposing factor. There are few studies that report HIV infection, diabetes mellitus, organ transplantation, and immunosuppressive therapy as the risk factors of splenic TB.[5-8]

Usually, isolated splenic TB has non-specific signs and symptoms, and the main presentation is a fever of unknown origin.[5,6,9] Other manifestations are malaise, weight loss, vague abdominal pain, and abdominal distention.[4,6,9,10] The most prevalent sign is splenomegaly.

Our patient had FUO and erythema nodosum which could be the manifestations of TB. The most common ultrasound findings of splenic TB are single or multiple focal hypoechoic lesions, splenic abscesses, calcifications, and isolated splenomegaly.[11] Our patient did not suffer from splenomegaly but multiple focal hypoechoic lesions. TST and QFT were negative in this case, but it must be considered that TST and QFT are not positive in all forms of TB, especially in pediatrics age.[12] One of the issues in this report is the first-time negative mycobacterium PCR on the spleen specimen despite pathologic report of granuloma with caseous necrosis. PCR test on tissue biopsy is neither 100% sensitive nor 100% specific for the diagnosis of TB, and combined inhibitory factors interfere in the detection of *M. tuberculosis* in stored material.[13] Caseous necrosis is characteristic but not pathogenomic of *M. tuberculosis* infection and several other diseases such as sarcoidosis, syphilis, and certain fungal infections such as histoplasmosis, cryptococcosis, and coccidioidomycosis may also cause caseous necrosis.[14] But, the important point is that when anti-TB treatment started, fever subsided; skin (erythema nodosum) and spleen lesions (micro abscess) disappeared in a period of time, and the general condition, as well as the appetite of the patient, became normal. In addition, repeating the PCR test was positive, which shows different sensitivity with different kits in different laboratories.

Usually, TB occurs after Crohn's disease secondary to immunosuppressive therapy resulting in acquired immunodeficiency,[15] but this is the first report of diagnosis of Crohn's disease after splenic TB diagnosis. However, it is likely that the patient initially suffered from Crohn's disease, but the main symptoms of the disease were manifested 3 months after the onset of TB diagnosis. If this hypothesis is correct, then probably, the immune deficiency of Crohn's disease, per se, not being secondary to immunosuppressive therapy, can be a predisposing factor for splenic TB. Another

hypothesis is that the patient was misdiagnosed, and the spleen lesions were initially due to Crohn's disease. It should be noted that although Crohn's disease, per se, may cause granuloma formation, caseous necrosis has not yet been reported with this disorder and our patient became asymptomatic, and the splenic lesions disappeared within 3 months only with anti-TB drugs.

Children with Crohn's disease present with a spectrum of systemic, gastrointestinal, and extra-intestinal manifestations.[16] It seems that fever, aphthous stomatitis, and erythema nodosum on the upper and lower limbs were the extra-intestinal manifestations of Crohn's disease in our case, while fever was a marker of systemic presentation. In addition, diarrhea was in concordance with gastrointestinal manifestations.

The patient had leukocytosis, anemia, and thrombocytosis in addition to increased ESR and CRP.

Although there are no pathognomonic laboratory tests for Crohn's disease, and normal laboratory tests cannot exclude the diagnosis of Crohn's disease, a complete blood cell count may reveal leukocytosis, chronic anemia, and thrombocytosis. In addition, children with Crohn's disease often have elevated inflammatory markers such as the erythrocyte sedimentation rate and C-reactive protein.[16]

It should be noted that some of the patient's clinical and paraclinical manifestations, such as fever, skin lesions, hematologic abnormalities, and increased acute phase reactants, were common between the two diseases of TB and Crohn's disease. In addition, there are no specific diagnostic criteria for Crohn's disease.[16] However, the diagnosis of Crohn's disease in our case was established by the combination of clinical, laboratory findings of colonoscopy and histopathologic analysis of colon biopsy.

Conclusion

The clinicians should be aware and consider an underlying disease such as IBD in unusual presentations of TB disease.

Ethical Approval

Written informed consent was obtained from the parents of patient for publication of this report.

Conflict of Interest

The authors declare no conflict of interest in this work.

References

1. Kansal S, Catto-Smith AG. Pediatric Crohn's disease: epidemiology and emerging treatment options. *Pediatric Health Med Ther* 2014;5:59-71. doi: 10.2147/phmt.s45509
2. Zhan F, Wang CJ, Lin JZ, Zhong PJ, Qiu WZ, Lin HH, et al. Isolated splenic tuberculosis: a case report. *World J Gastrointest Pathophysiol* 2010;1(3):109-11. doi: 10.4291/wjgp.v1.i3.109
3. Standardized Assessment Tools for Pediatric IBD patients. https://www.crohnscolitisfoundation.org/sites/default/files/legacy/science-and-professionals/programs-materials/ibd-nurses/best-practices/pediatric-assessment-nov.pdf. Accessed March 27, 2022.
4. Kumar S, Pai AG, Tungenwar PN, Bhandarwar AH. Isolated primary tuberculosis of spleen-a rare entity in the immuno-competent patient. *Int J Surg Case Rep* 2017;30:93-6. doi: 10.1016/j.ijscr.2016.11.038
5. Azzam NA. Splenic tuberculosis presenting as fever of unknown origin with severe neutropenia. *Ann Clin Microbiol Antimicrob* 2013;12:13. doi: 10.1186/1476-0711-12-13
6. Masoodi I. Splenic tuberculosis: report of two cases and literature review. *Br J Med Pract* 2017;10(1):a1001.
7. Gupta PP, Fotedar S, Agarwal D, Sansanwal P. Tuberculosis of spleen presenting with pyrexia of unknown origin in a non-immunocompromised woman. *Lung India* 2008;25(1):22-4. doi: 10.4103/0970-2113.44134
8. Rampton DS. Preventing TB in patients with Crohn's disease needing infliximab or other anti-TNF therapy. *Gut* 2005;54(10):1360-2. doi: 10.1136/gut.2005.076034
9. Dixit R, Arya MK, Panjabi M, Gupta A, Paramez AR. Clinical profile of patients having splenic involvement in tuberculosis. *Indian J Tuberc* 2010;57(1):25-30.
10. Kundu PR, Mathur SK, Singh S, Duhan A, Aggarwal G, Sen R. Isolated tuberculous splenic abscess in an immunocompetent individual. *Asian Pac J Trop Med* 2011;4(1):81-2. doi: 10.1016/s1995-7645(11)60040-0
11. Sharma SK, Smith-Rohrberg D, Tahir M, Mohan A, Seith A. Radiological manifestations of splenic tuberculosis: a 23-patient case series from India. *Indian J Med Res* 2007;125(5):669-78.
12. Sayyahfar S, Karimi A, Fahimzad A, Shamshiri AR. Comparison of tuberculin skin test result and interferon gamma response to human PPD in BCG scar positive and negative children. *J Epidemiol Glob Health* 2014;4(1):45-50. doi: 10.1016/j.jegh.2013.09.002
13. Barcelos D, Franco MF, Leão SC. Effects of tissue handling and processing steps on PCR for detection of *Mycobacterium tuberculosis* in formalin-fixed paraffin-embedded samples. *Rev Inst Med Trop Sao Paulo* 2008;50(6):321-6. doi: 10.1590/s0036-46652008000600002

14. Güler M, Şimşek A, Ofluoğlu R, Çelenk Ergüden H, Çapan N. Are all granulomatous lesions tuberculosis? *Respir Med Case Rep* 2012;5:42-4. doi: 10.1016/j.rmedc.2011.10.001
15. Cappello M, Randazzo C, Rizzuto G, Bonura C, Di Vita G, Galia M. Splenic tuberculosis in a patient with Crohn's disease on infliximab: case report. *Inflamm Bowel Dis* 2010;16(3):368-70. doi: 10.1002/ibd.20998
16. Higuchi LM, Bousvaros A. Clinical Presentation and Diagnosis of Inflammatory Bowel Disease in Children. Up To Date; 2022. Available from: https://www.uptodate.com/contents/clinical-presentation-and-diagnosis-of-inflammatory-bowel-disease-inchildren?search=Clinical%20presentation%20and%20diagnosis%20of%20inflammatory%20bowel%20disease%20in%20children&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed 27March 2022.