A Case of Tuberculous Colitis with Associated Takayasu’s Arteritis

Rajiv Baijal¹, Arun Chogle², Praveen Kumar¹, Nimish Shah¹, Sandeep Kulkarni¹, Soham Doshi¹, Deepak Gupta¹, Deepak Amarapurkar¹

Abstract

Intestinal tuberculosis and Crohn’s disease (CD) are two different granulomatous diseases affecting the intestinal tract with similarities in clinical presentation but different therapeutic strategies. Takayasu’s arteritis (TA) is a granulomatos disease of aorta and its major branches. TA is associated with tuberculosis as well as CD. We present a case of Granulomatos colitis in a young female who was detected to have TA. She was initially diagnosed as a case of CD elsewhere four years previously and has been on immunosuppressive treatment. Repeat evaluation at our centre using endoscopic, radiological and histological criteria suggested a diagnosis of intestinal tuberculosis which was confirmed both by molecular biology techniques as well as by tissue cultures for mycobacterium tuberculosis. Herein we discuss the diagnostic challenge of distinguishing intestinal tuberculosis and CD in a tuberculous endemic country like India. Recent studies have analysed the immunological mechanisms explaining the association of TA and tuberculosis. These studies are important as they may give a clue for better targeted therapies and out come in TA.

Introduction

Distinguishing tuberculosis and Crohn’s disease (CD) in a patient presenting with chronic abdominal pain and diarrhoea is a huge diagnostic challenge, particularly in a tuberculous endemic countries.¹ In this report, we describe a young female patient in her 20s who was diagnosed as a case of CD four years earlier elsewhere and referred to our unit for evaluation for repeated relapses of CD. We suggest a repeat diagnostic evaluation of a case of CD is important particularly in those with a long history of disease.

Case Presentation

A 21-year female presented with diarrhoea, abdominal pain and fever for one and half months. She had 8-10 watery, large volume, non-bloody stools per day associated with evening rise of fever. She also had pain in right iliac fossa without nausea, vomiting or abdominal distension. During last 6 weeks she had lost 7 kg of weight. She did not have joint pain, back pain, eye complaints or jaundice.

She had a past history of similar complaints for last four years. She was diagnosed as a case of Crohn’s Disease (CD) on the basis of colonoscopy findings (multiple aphthous ulcer in ileo-caecal region) and histopathology (chronic lymphocytic inflammatory infiltrate, no granuloma) at a tertiary centre 4 years back. At that time acid fast bacilli...
Fig. 1: Multiple circumferential ulcers

smear and cultures were negative. Chest X-ray, Mantoux test was negative for tuberculosis. She had two relapses of CD in the form of diarrhoea which were treated with oral steroids. There was no history of fever during the previous relapses. After remission she was maintained on azathioprine and 5-aminosalicylic acid (5-ASA). There was no past history or contact with a case of TB.

On examination she was febrile (temperature – 102°F). She had absent pulses in the right upper limb with non recordable blood pressure in right upper limb. Blood pressure was 100/70 mm Hg in left upper limb and 104/70 mm Hg in both lower limbs. Rest of the systemic examination was normal.

Investigations revealed haemoglobin -10.5 gm/dl, WBC count - 6100/cu.mm with 70% neutrophils and 30% lymphocytes, platelets – 295000/cumm, erythrocyte sedimentation rate at 1 hour was-90 mm, Serum C-reactive protein was 75.2 mg/dl (0-10 mg/dl). Liver profile and renal function tests were normal. Mantoux test was negative (less than 5 mm). Chest X-ray was normal. Ultrasonography of abdomen revealed mild thickening in the terminal ileum with no obvious lymphadenopathy or free fluid. Colour Doppler imaging of both upper limbs showed reduced flow in right subclavian artery, no thrombus was detected. Left subclavian artery and other blood vessels showed normal blood flow. Two-dimensional echocardiography did not reveal any abnormality.

Computed Tomography (CT) enteroclysis showed thickening of ileal loops, mural enhancement and increased density of perienteric fat. No lymph nodes or free fluid was evident. Magnetic resonance angiography (MRA) showed narrowing in the right subclavian artery without any thrombus suggestive of vasculitis. Rests of the vessels were normal.

Her autoimmune profile including (ANA, ds-DNA, p-ANCA and c-ANCA), and treponema pallidum haemagglutination (TPHA) were negative.

Colonoscopy showed multiple circumferential ulcers in the caecum and terminal ileum with size from few mm to 2 cm with deformed ileo-caecal valve (Figure 1). Biopsy showed marked lymphocytic infiltrate. No evidence of granuloma or dysplasia was present on histopathology. Paraffin embedded biopsy specimens were tested for mycobacterial tuberculosis complex using Real time polymerase chain reaction (PCR by mycoreal test with highly specific probes). Löwenstein-Jensen (LJ) medium culture for tuberculosis was awaited.

She was given sulphasalazine (2 gm/day), aspirin (75 mg/day) in view of vasculitis and azathioprine (100 mg/day) was continued. Though her TB-PCR report was positive, anti-tuberculous treatment (ATT) was not initiated pending her mycobacterial TB culture report. Her fever subsided with 5-ASA and azathioprine treatment and was discharged with the same medication and was asked to follow up after 8 weeks.

On her next visit, she was in remission. Meanwhile her LJ medium culture report was positive for mycobacterium tuberculosis. So we started four drug anti TB treatment(ATT) consisting of isoniazid (INH-5 mg/kg), rifampicin (10 mg/kg), ethambutol (15 mg/kg) and pyrazinamide (20 mg/kg). After 2 months this was reduced to two drug regimen of INH and rifampicin. Azathioprine, sulphasalazine and aspirin were also continued. She was then asked to continue this treatment for another 10 months and to follow-up.

After 1 year of ATT she remained asymptomatic. Treatment for CD was continued which included azathioprine, sulphasalazine and aspirin. When last seen CD was in remission. Her pulses in right extremities were now palpable. Colonoscopy at this stage was normal. She is being monitored for relapses.

Discussion

A variety of clinical, endoscopic and radiological criteria have been recommended for the differentiation of TB and CD, but these criteria have been demonstrated to have their limitations too. Although the age and sex distribution of these diseases are similar, the total duration of symptoms in patients with diagnosis of CD is usually longer than that of tuberculosis. Endoscopically, the distribution of macroscopic lesions are similar in the two conditions, with 60-70% of the patients showing ileocaecal involvement and about 50% showing involvement of the transverse or distal colon. Involvement of the ileocaecal valve, deformity of the caecum and stricture/stenosis are more common in the TB patients, while fistulae are more common in patients with CD.
In our patient, repeat endoscopic evaluation done 4 years after onset of symptoms showed ulceration in ileocaecal region without demonstration of granulomas, absence of caseation and confluence in the submucosa. The type and frequency of granulomas, presence or absence of ulcers lined by epithelioid histiocytes and microgranulomas, and the distribution of chronic inflammation have been identified as histological parameters that can be used to differentiate TB and CD in mucosal biopsy specimens obtained at colonoscopy. In view of absence of typical macroscopic and microscopic features of intestinal TB, the tissues were sent for RT-PCR for TB complex as well as for mycobacterial culture.

TB has been diagnosed by performing PCR on body fluids (sputum, pleural fluid, ascitic fluid, CSF and blood), tissues (pleural, peritoneal, intestinal, joint, skin, bone marrow, lymph node and pancreas) and cells (peripheral blood mononuclear, endothelial, fibroblast). In a previous study carried out at our institution, 60 cases of diagnosed intestinal tuberculosis and 20 Crohn’s disease were compared using clinical data, radiological and endoscopic findings. Test for detection of Mycobacterium tuberculosis complex was the Gen-Probe (USA) Amplified Mycobacterium tuberculosis direct test by PCR assay. Oligonucleotide primers for detection of Mycobacterium tuberculosis were selected to amplify a 123 base pair (bp) fragment of the 5’ portion of IS 6100, which is specific for Mycobacterium tuberculosis and contains an internal endonuclease site that allows confirmation of the product by digestion of the endonuclease. PCR assay showed sensitivity, specificity, positive and negative predictive values in this study were 21%, 95%, 92% and 28% respectively.

More recently RT-PCR technology is used for detection of TB. The limitation of RT-PCR is that it detects only mycobacterium tuberculosis complex and not mycobacterium avium or other environmental mycobacteria. For the last several years mycobacterium avium subspecies paratuberculosis (MAP) have been implicated as an aetiological agent in CD. The PCR assay for MAP targets DNA insertion element IS-900. The PCR method we used detects IS-6110 insertion sequence of mycobacterium tuberculosis complex.

Even though RT-PCR was positive in our patient, we did not immediately start ATT for the following reasons. 1) patient was diagnosed as a case of CD in a tertiary referral centre based on endoscopic, histological, radiological and negative microbiological findings. 2) When the patient was seen in our centre, the patient was found to have co-existing TA satisfying The American College of Rheumatology 1990 criteria for the classification of Takayasu’s arteritis. In the same individual is rare, but is being increasingly reported in part owing to heightened awareness and better access to superior diagnostic imaging. 4) HLA genotype links and even infectious agents such as Mycobacterium tuberculosis have been implicated as common aetiologies, but to date no definite aetiological associations have been identified. 5) RT-PCR positive in our patient detected only mycobacterium tuberculosis complex which includes besides mycobacterium tuberculosis other pathogenic mycobacteria which have different sensitivity to ATT as in the case of mycobacterium bovis which is known to be pyrazinamide resistant.

Culture report available eight weeks after, confirmed that patient had mycobacterium tuberculosis. We could not find similar case in literature in whom coexistent CD, TA and culture positive intestinal tuberculosis was detected in same patient and hence we are reporting this case.

In our patient, after the start of ATT, her right radial pulse gradually returned and was minimally weaker than the left. However we did not repeat MR angiography to confirm the improvement in the circulation in the right upper limb. This finding has also been reported in paediatric patient of TA with tuberculosis cervical adenitis who demonstrated complete symptomatic remission as well as return of pulses with simultaneous ATT. However this finding was not confirmed by other authors.

The temporal relationship between diagnosis of TA and active intestinal tuberculosis in our patient suggests a link between TA and tuberculosis. Research papers on this aspect have been published during the last two decades. Broadly these can be categorised under two headings.

A. Humoral and cellular immune response to mycobacterial antigens.
B. Serum cytokine profiles and their relationship to disease activity of TA.

Expression of heat shock protein (HSP)-65 as well as infiltrations of T-cells in arterial lesions are important in the pathogenesis of TA.

Recent studies have demonstrated IgG antibodies to mycobacterial HSP -65 (mHSP-65) and its human homologue ( hHSP60) suggesting that cross reactivity of immune response between mHSP65 and hHSP60 or related arterial antigens may be an important cause of development of autoimmunity in TA.

In addition proinflammatory cytokines including interleukin -18 and TNF-α have been contributed to immunity against M. tuberculosis infection and the formation of granulomas. Interleukin 18 and TNF-α are also up-regulated in patients with TA. Therefore the elevated levels of these cytokines in tuberculosis may potentially contribute of the development of TA in susceptible host. Further elucidation of the nature
of the relationship between TA and tuberculosis may lead to the development of more targeted therapies and better outcomes for TA patients.\textsuperscript{13}

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**References**