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Alimentary Tract

Serial C-reactive protein measurements in patients treated for suspected abdominal tuberculosis

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ABSTRACT

Background: Response to treatment is often used as a criterion for the diagnosis of abdominal tuberculosis.
Aim: To determine utility of serum C reactive protein (CRP) in assessment of response to anti-tubercular therapy (ATT) in abdominal tuberculosis (ATB).
Methods: We retrospectively analysed the database of patients with suspected ATB (intestinal and/or peritoneal). Response to ATT was assessed using subjective and objective (ulcer healing or ascites resolution) parameters. Serum CRP levels were estimated at baseline and then at 2 months and 6 months of ATT.
Results: One hundred and twelve patients were included in the analysis. The mean age was 36.57 ± 15.04 years and 54.46% (61/112) were males. Sixty-six patients (58.92%) had intestinal, 28 (25%) had peritoneal and 18 (16.07%) had both. Eleven patients had a normal CRP at baseline while 101 had elevated levels. The CRP levels declined in 94 patients at 6 months. One patient with increased levels at 2 months had multi-drug resistant TB. Seven patients showed elevated or plateaued CRP levels on follow-up. These patients had underlying Crohn's disease (3 patients), peritoneal carcinomatosis (1), inter-current infection (1), lymphoma (1) and non-healing ulcers (1).
Conclusion: Lack of decline in CRP may suggest alternative diagnosis or drug-resistant tuberculosis.

1. Background

Abdominal tuberculosis is an important clinical problem for clinicians in the tropical world. Abdominal tuberculosis is often difficult to diagnose because of several close differential diagnoses like inflammatory bowel disease and intestinal malignancies (for intestinal tuberculosis) and peritoneal carcinomatosis (for tubercular ascites) [1,2]. The microbiological diagnosis is often not feasible because of the low sensitivity of microbiological tests (acid-fast bacilli staining or culture or polymerase chain reaction). Many patients are initiated on empirical anti-tubercular therapy (ATT) and an adequate response to ATT is recognized as a criterion for the diagnosis of abdominal tuberculosis [1,3]. The assessment of response to therapy includes subjective (resolution of symptoms like abdominal pain, abdominal distension, fever, weight gain and the return of appetite) as well as objective parameters (healing of intestinal ulcers on colonoscopy or resolution of ascites on ultrasound) [1]. Symptomatic clinical response (in absence of an objective response) may occur with use of ATT in other diseases like the Crohn's disease [1]. The utility of biomarkers (like CRP) for follow-up in abdominal tuberculosis is not known and it is uncertain if changes with treatment would mirror the objective response to therapy in patients with abdominal tuberculosis [4–7].

Various inflammatory biomarkers, like C reactive protein (CRP), neopterin, beta 2 microglobulin etc., have been used for the assessment of treatment response, presence of disseminated disease with high mycobacterial load, prediction of persistent culture positivity, radiological resolution, higher mortality and for differentiation of tuberculosis from malignancy [8–13]. CRP is a non-specific acute phase reactant produced by the hepatocytes in various inflammatory conditions. It binds to the phosphocholine moiety of dead or dying cells of bacteria/viruses and helps in complement medi-

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ated phagocytosis thus having a role in innate immunity [14,15]. The utility of this biomarker for assessment of response to ATT in patients with abdominal tuberculosis has not been reported previously. In this study, we report the utility of serial measurements of CRP in the prediction of objective response in patients with abdominal tuberculosis.

2. Methods

2.1. Setting

This study is a retrospective analysis of collected database of adult patients who attended a large tertiary care center in North India and received ATT for a suspected diagnosis of abdominal tuberculosis (ATB). The study protocol was cleared by institute ethics committee of the Postgraduate Institute of Medical Education and Research at Chandigarh and the need for informed consent was waived off in view of the retrospective nature of the study. All patients who underwent invasive procedures (like colonoscopy) provided written informed consent prior to the procedure.

2.2. Diagnosis

We recorded the clinical presentation, radiological findings and the biochemical parameters in a proforma. All patients with suspected abdominal tuberculosis (intestinal, peritoneal or both) who received ATT and had complete data were included in the analysis. A patient was defined to have abdominal tuberculosis when along with clinical and radiological features there was:

1) Evidence of acid-fast bacilli (AFB) on smear or culture of tissue/fluid (Confirmed tuberculosis)
2) Presence of caseating granulomas on histology (Confirmed tuberculosis)
3) Epithelioid granuloma with chronic inflammation or ascitic fluid adenosine deaminase (ADA) levels >32 U/L (Clinically diagnosed case)
4) Demonstration of objective response to ATT with evidence of ulcer healing or ascites resolution (Clinically diagnosed case)

2.3. Patient follow-up

All patients initiated on ATT for a diagnosis of abdominal tuberculosis were closely followed up. This included monthly assessment of the clinical symptoms e.g. weight gain, defervescence of fever, resolution of abdominal pain and/or distension and general well-being. The patients were also evaluated for evidence of objective response. For this, the patients with intestinal tuberculosis underwent repeat colonoscopy for assessment of mucosal healing (resolution of ulcers or reduction in their size/number) after initiation phase of the ATT i.e after 2 months. The patients with peritoneal tuberculosis underwent an abdominal ultrasound at two months for documentation of resolution or reduction in the ascites. Those showing evidence of objective response were continued on ATT. In patients with suspected intestinal tuberculosis who had persistent ulcers at 2 months after ATT, a re-evaluation with intestinal biopsy for histological evaluation and microbiological testing for drug-resistant tuberculosis was done. Serial measurements of CRP at start of ATT and subsequently at 2 and 6 months of follow up were also done. CRP levels of <6 mg/L were considered as normal. The decline in CRP levels was sought for and compared with the objective response to treatment. In patients who had either a plateauing of CRP levels or an increase in CRP levels, the underlying causes were evaluated.

Table 1
Profile of patients with abdominal tuberculosis.

Parameter	Finding N and%
Mean age	36.57 ± 15.04 years
Male	54.46% (61/112)
Clinical features	
Abdominal pain/discomfort	(110/112) 98.21%
Loss of weight	(93/112) 83.03%
Loss of appetite	(91/112) 81.25%
Fever	(70/112) 62.5%
Intestinal obstruction	(45/112) 40.14%
Diarrhoea	(14/112) 12.5%
Lump abdomen	(11/112) 9.82%
Bleeding per rectum	(08/112) 7.14%
Comorbidities	(22/112) 19.64%
	Cirrhosis: 4, Diabetes mellitus: 4, Hypothyroidism: 3, Seizure disorder: 2, Chronic pancreatitis: 1, COLD: 1, BPH: 1, CHB: 1, CHC: 1, CKD: 1, GSD: 1, EHPVO: 1, Hypertension: 1, HIV: 1, Scoliosis: 1
Mantoux positive	(64/112) 57.14%

COLD: chronic obstructive lung disease; BPH: benign prostatic hyperplasia; CHB: chronic hepatitis B; CHC: chronic hepatitis C; CKD: chronic kidney disease; GSD: gall stone disease; EHPVO: extrahepatic portal venous obstruction.

3. Results

Of the 122 patients recorded in the database over a period of 2 years, 10 patients had missing/incomplete data and hence were excluded from the study. The remaining 112 patients formed the study cohort. The clinical spectrum of these patients is provided in Table 1. Of the 112 patients, 25 (22.32%) patients had confirmed ATB while 87 (77.68%) were clinically diagnosed cases. Sixty-six patients (58.92%) had intestinal involvement, 28 (25%) had peritoneal and 18 (16.07%) had both intestinal and peritoneal involvement. Serum-ascites albumin gradient (SAAG)/adenosine deaminase (ADA) values were available for 34 patients. Thirty-one patients had low SAAG and high ADA (91.17%). Three patients who had high (>1/1 g/dL) SAAG had underlying cirrhosis with portal hypertension.

At the initiation of ATT, 11(9.82%) had normal CRP levels. All of these 11 patients had intestinal involvement while 1 patient also had minimal ascites. These patients were started on ATT and all except 3 showed clinical and objective response with ulcer healing documented after 2 months of ATT. One patient developed an elevation in CRP levels at around 6 weeks of ATT during an episode of intestinal obstruction and was treated with surgical resection of the diseased area with primary anastomosis. Rest of the two patients were eventually diagnosed to have Crohn's disease and NSAID related enteropathy respectively (Fig. 1).

Of the 101 patients with elevated CRP levels, the mean values of CRP at baseline, 2 months and 6 months were 53.11 ± 36.54, 12.33 ± 17.97 and 5.99 ± 14.80, respectively. At 2 months of ATT, 52 (51.48%) patients had normalization of CRP and all of these continued to have normal values at 6 months. Of the remaining 49 patients, 42 patients had a decline in CRP levels at 2 months. Of the 7 with plateaued or elevated levels at 2 months, one was a 29-year-old male who had evidence of drug-resistant tuberculosis in the form a positive GenXpert for rifampicin resistance from intestinal biopsy at 2 months. He was started on DOTS-plus regimen and showed evidence of mucosal healing and normalization of CRP (at 6 months) after modification of ATT. Of the remaining 6 patients with elevated CRP at 2 months, all continued to have an elevated CRP at 6 months.

Ninety-one patients had complete normalization of CRP levels at 6 months. Three patients had a slight elevation of CRP at 6 months but demonstrated a declining trend over these three time periods (0, 2 and 6 months) and had a clinical and objective response. Over-

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