The Role of Serum Bio-Markers in Predicting Small Bowel Pathology in Crohn`s Disease Patients

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Abstract: *Background:* Computed tomography enterography (CTE) is a useful modality in the evaluation of small bowel (SB) crohn`s disease (CD) as it can provide assessment of disease activity, extramural abnormalities and SB complications. This procedure however utilises radiation exposure. The aim of this retrospective study was to determine the clinical indications and findings on CTE and to determine if serum bio-markers (CRP, ESR, platelet count and anaemia) can predict significant pathologies.

Method: This was a retrospective analysis where 50 patients above the age of 18 with CD who had CTE between October 2013 and February 2015 were identified. The clinical indications, serum bio-markers and CTE findings in these patients were analysed.

Results: The main indications for CTE were abdominal pain/discomfort and/or symptoms suggestive of SB obstruction. 26% of CD patients had active inflammation, 36% had a SB stricture and 4% had active inflammation with stricturing and fistulating disease. All the patients with a completely normal CTE did not have a raised bio-marker whist 76.9% of patients with active inflammation had one or more positive bio-markers. Additional findings were active colitis (8%), splenomegaly (4%), aortitis (2%) and had sacroileitis (2%). In these patients, 75% had a positive bio-marker. In patients with positive findings, the Erythrocyte Sedimentation Rate (ESR) was the most common marker of inflammation.

Conclusion: CTE is an important tool in management of patients with CD however, in the presence of normal biomarkers, clinicians should question the need for CTE and thus decrease exposure of CD patients to ionising radiation.

Keywords: Computed tomography enterography, Crohn's disease, Serum bio-markers, Small bowel pathology.

INTRODUCTION

Crohn's disease (CD) is characterized by a chronic, focal, discontinuous granulomatous transmural inflammation. Management of CD requires assessment of the location, extent, activity and severity of inflammatory lesions and of any potential complications [1]. A diagnosis is usually obtained through histological analysis of biopsies taken during endoscopy [2]. However, further radiological imaging, particularly of the small bowel (SB), may be required. This usually takes the form of cross sectional imaging since the length of the SB makes it cumbersome to perform a panenteroscopy on all patients with suspected SB disease. Capsule endoscopy (CE) can be used to assess and screen the SB for CD related pathology. However, the risk of capsule retention in patients with CD is 5-13% [3].

SB assessment can also be done through computed tomography enterography (CTE) [4]. The technique of CTE is a combination of small bowel distension using a neutral or low-density oral contrast mixture with an abdomino-pelvic CT (computed tomography) examination during the enteric phase following administration of intravenous contrast [5]. The advantages of CTE are that it can be easily performed, is well tolerated by patients, allows comparison with previous cross-sectional imaging, is operator-independent and allows simultaneous assessment for extra-luminal manifestations. This makes it one of the investigations of choice in cases of suspected SB stricture [5, 6]. In established disease, CTE can help in selecting treatment and assessing response [1]. It is, however, less sensitive than CE in detecting early mucosal abnormalities and it utilises ionising radiation [5].

In CD, CTE may identify active inflammation, fibrostenosing disease and complications such as fistulae or abscesses. Features of active inflammation include mural hyperenhancement, mural thickening and stratification, transmural ulceration, engorged vasa recta and increased attenuation of mesenteric fat [6, 7]. A study on resected pathological specimens of patients with CD showed a good correlation between findings suggestive of inflammation or fibrostenosing disease seen on CTE and inflammatory changes seen in the pathological specimens [8].

The major drawback with CTE is that it requires exposure to ionising radiation. Patients with CD are relatively young and may undergo repeated

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investigations due to the chronic, relapsing nature of CD. It is estimated that 1.5-2% of all cancers in the USA may be caused by radiation exposure [9]. CT accounts for 16.2% of imaging studies in patients with CD and for 77.2% of diagnostic radiation [10]. Another study showed that CT exposures were estimated to produce 0.7% of total expected baseline cancer incidence and 1% of total cancer mortality [11]. Other drawbacks include the potential contrast toxicity and the need to drink large volumes of fluid over a short period of time so as to achieve luminal distension.

Laboratory blood investigations can be associated with active CD. The most common changes in the complete blood count related to CD are anaemia and thrombocytosis [2]. Anaemia has been associated with active CD however its aetiology can be multifactorial (iron, folate or Vitamin B12 deficiency, myelo-suppression, haemolysis and inflammation) [12]. C Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) are other markers of inflammation. CRP is the most studied inflammatory marker and correlates well with disease activity, with a sensitivity of 70-100%. It has a short half-life (about 19 hours) and thus rises early after the onset of inflammation and rapidly declines after resolution of the inflammation [13]. Studies have shown that when correlating CRP with CTE findings, CRP correlates mostly with increased attenuation of mesenteric fat [14]. ESR is the rate at which erythrocytes sediment over one hour and so will be higher in inflammation due to a slower rate. It reaches a peak less rapidly and declines over several days, even if the inflammation has ameliorated [15]. ESR correlates better with colonic, rather than ileal, disease [15].

However, (1) in the absence of an ideal bio-marker for active CD, (2) the presence of symptoms in patients with CD which could be due to the disease itself or other gastrointestinal pathology and (3) the availability and reliability of CTE, the latter test is very often requested. The aim of this retrospective study were (1) to analyse the indications and findings on CTE (2) and to correlate the findings on CTE with blood biochemical bio-markers (CRP, ESR, haemoglobin and platelets) as to positively identify which patients would benefit mostly from this tests as to decrease their radiation exposure.

METHOD

This was a retrospective analysis where 50 patients above the age of 18 with CD who had CTE between October 2013 and February 2015 were identified through the Medical Imaging department. The clinical indications, serum biochemical markers and CTE findings in these patients were analysed. Active inflammation was deemed to be present if one or more of the following were present: wall thickening, mural hyperenhancement, enlarged lymph nodes and increased vascularity. All the CTE were interpreted by the same radiologist.

The chosen blood bio-markers were haemoglobin, platelet count, ESR and CRP. Anaemia was considered to be present at haemoglobin levels of less than 11.5g/dL in females and less than 13g/dL in males, as these are the lower limit of the laboratory range at our laboratory. The cut-off for the platelet count was $400x10^9$/L. The CRP was considered to be positive if it was more than 6mg/L. The cut-off value for the ESR depended on the patient's gender and age [16]. The presence of anaemia, raised platelet count, ESR and CRP were considered as positive bio-markers.

RESULTS

Radiological Studies

Fifty CTE studies of CD patients were identified and analysed. Their mean age was 43.5 years (18-75 years). Fifty-eight per cent (58%) of patients were female. The main indications for CTE were (1) to assess and determine the extent and degree of SB involvement due to persistent gastrointestinal symptoms which were clinically suggestive of SB pathology (68%), (2) to assess for small bowel obstruction in CD patients with signs and/or symptoms suggestive of obstruction (22%), (3) intestinal biopsies suggestive of but not conclusive for CD (8%) and (4) to assess extent of SB inflammation prior to commencing anti-tumour necrosis factor alpha treatment (2%).

SB pathology was present in 66% of patients. Active SB inflammation was present in 26%, a SB stricture was present in 36% and 4% had active inflammation with associated SB stricturing and fistulating disease. Two patients with an inflammatory stricture developed small bowel obstruction.

No small bowel pathology was present in 34% of patients. However within this group of patients there were other significant findings. These were active colitis (8% of total), splenomegaly (4% of total), aortitis (2% of total) and sacroileitis (2% of total).

Serum Bio-markers

The serum bio-markers (haemoglobin, platelet count, ESR and CRP) were analysed for all the patients and compared to the radiological findings. Figure **1** best depicts the correlation between the radiological findings and serum bio-markers. The majority (76.9%) of patients with active inflammation had one or more positive bio-markers, this being 75% for patients with stricturing or fistulating disease. All the patients with a completely normal CTE did not have a raised bio-marker. 75% of patients with an additional finding (colitis, splenomegaly, aoritis or sacroileitis) had a positive bio-marker. Table **1** demonstrates the positive and negative predictive values for each serum bio-marker.

In patients with positive findings, the ESR was the most common marker of inflammation. It was elevated in 69.2% of patients with active inflammation and 60% of patients with stricturing or fistulating disease. It was raised in 75% of patients with other intra-abdominal findings and was not raised in any patient with a completely normal CTE. The CRP was positive in 38.5% of patients with active inflammation, in 50% of those with stricturing and fistulating disease and in 37.5% of patients with additional intra-abdominal findings. Anaemia was present in 30.8% of those with active inflammation, 45% of those with stricturing and fistulating disease and 25% of those with additional intra-abdominal findings. Thrombocytosis was present in 23.3% of patients with active inflammation, 20% of patients with stricturing and fistulating disease and 25% of patients with additional intra-abdominal findings.

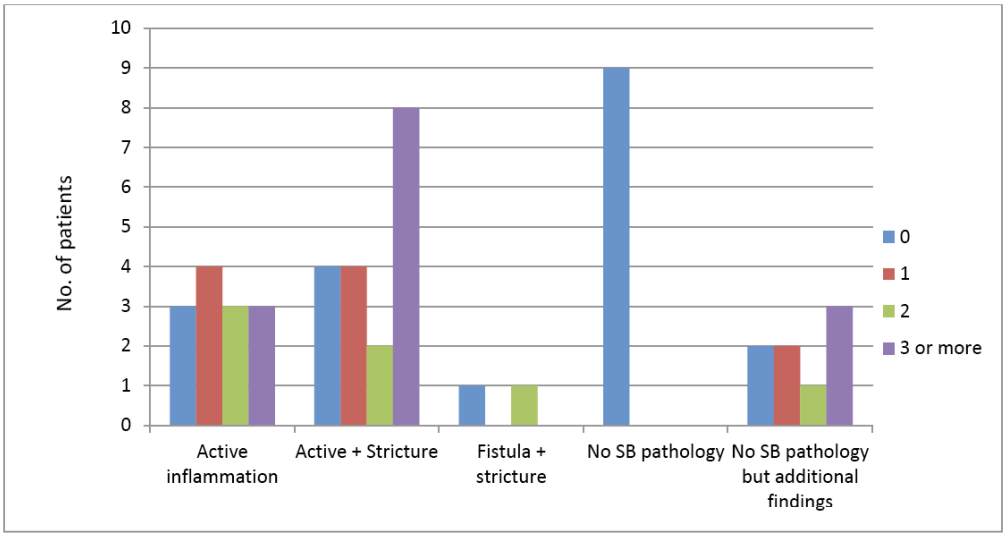

Figure 1: A graph demonstrating the number of positive bio-markers of inflammation (0, 1, 2 or 3 or more) and the CTE findings. SB- small bowel.

Table 1: A Table Showing the Positive and Negative Predictive Values for Small Bowel Pathology for Each of the Biomarkers Investigated

Serum Bio-Marker	Predictive Value	Percentage
Erythrocyte sedimentation rate	PPV for SB pathology	100%
	NPV for SB pathology	43%
C-Reactive Protein	PPV for SB pathology	100%
	NPV for SB pathology	33%
Anaemia	PPV for SB pathology	100%
	NPV for SB pathology	30%
Thrombocytosis	PPV for SB pathology	100%
	NPV for SB pathology	26%

PPV – Positive Predictive Value; NPV – negative predictive value, SB – small bowel

None of the patients with a completely normal CTE had a positive bio-marker.

DISCUSSION

CTE is useful in assessing for active inflammation, fibrostenosing disease and complications associated with CD such as fistulae or abscesses. Its use is limited by patient exposure to ionizing radiation. The majority (76.9%) of patients who had active inflammation in our study group had one or more raised inflammatory markers. 75% of patients with stricturing and/or fistulating disease had one or more positive markers. Most of the patients in the study group were relatively young. Clinicians must consider the cumulative radiation dose when selecting investigations. When possible, dose reduction techniques should be applied in CTE image acquisition protocol [6]. Other imaging investigations that are of value in CD include ultrasonography, magnetic resonance enterography (MRE), nuclear medicine techniques such as white blood cell scintigraphy and CE. MRE provides cross-sectional imaging with similar diagnostic accuracy to CTE without exposing the patient to ionising radiation [1]. Its main drawbacks are that it is usually less available, is more time-consuming and might not be accepted by claustrophobic patients.

One of the limitations of this study could be the relatively small numbers of CD patients. However, we think that there was definitely an important outcome as we have demonstrated that all patients with a completely normal CTE had no positive blood bio-marker identified. Another limitation of this retrospective study is the lack of the faecal bio-marker calprotecin. Being a retrospective study we did not have a faecal calprotectin (FC) for each patient. Only 38% of patients had a FC. However, although the important role of FC in inflammatory bowel disease has been demonstrated, there are still some unanswered questions. The optimal cut-off value of FC which predicts remission is still to be determined as various studies report varies levels from 56-340mg/kg.[17,18] Other studies have demonstrated a limited role for FC in determining SB pathology [19, 20]. All this is also demonstrated by the FC in our study group. For patients with SB pathology (inflammation and inflammatory stricturing), 5.3% had an FC of < 50mg/kg, 15.8% had an FC value between 50-200mg/kg and in 36.8% the level was > 200mg/kg. For patients with no SB pathology, none had an FC level <50mg/kg. An elevated FC of between 50-200mg/kg was present in 26.3% of patients and 15.8% had a level of > 200mg/kg. This group of patients did not have any evidence of active colonic disease.

CONCLUSION

CTE is a valuable technique in detecting active and complicated small bowel CD. In CD patients, due to their young age and risk of radiation exposure, the presence of normal serum bio-markers should alert the clinician to question the real need for CTE. Other investigations such as capsule endoscopy with patency capsule and/or MRE should be considered as alternatives.

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