

^{99m}Tc-MDP abdominal scintigraphy in a paediatric case of GI protein loss - A viable and simple alternate to HSA imaging

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ABSTRACT

A nine-month old male child presented with low-grade fever, loose stools and facial puffiness. Clinically patient was otherwise normal except for a firm liver on palpation. The laboratory tests revealed hypoproteinemia (both albumin and globulin) and iron deficiency anemia. Differential diagnosis considered were: 1. Nephrotic syndrome, 2. Cystic fibrosis (in view of recurrent diarrhea and respiratory complaints) 3. Chronic liver disease, in view of firm palpable liver 4. Lastly protein losing enteropathy (PLE). As biochemically patient revealed no positive results, PLE was suspected. For confirmation ^{99m}Tc-Methylene diphosphonate (MDP) scintigraphy was found to be useful in the setting of non availability of ^{99m}Tc-HSA. MDP scan revealed abnormal minimal extravasation of tracer from bowel loops in right lower abdominal quadrant suggesting a diagnosis of PLE. According to the American Gastroenterological Association (AGA) in patients with iron-deficiency anemia who do have GI symptoms, the prevalence of celiac disease is higher and ranges from 10% to 15% which may be a plausible explanation in our patient. The diagnosis of PLE is most commonly based on the determination of fecal alpha-1 antitrypsin clearance. However the localization of gastrointestinal protein (GI) protein loss is possible by scintigraphic techniques alone, as was done in our case using ^{99m}Tc-MDP instead of conventionally used ^{99m}Tc-HSA.

Key words: ^{99m}Tc-MDP scintigraphy; Protein losing enteropathy; Iron deficiency anemia, Celiac disease

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INTRODUCTION

PLE is a clinical condition associated with excess protein loss into the gastrointestinal

lumen leading to hypoproteinemia. It is commonly seen in many malignant and benign conditions like ulcerative colitis, regional enteritis, Whipple's disease, tropical sprue, gastric carcinoma. Furthermore, diseases such as constrictive pericarditis, congestive heart failure, intestinal lymphangiectasia, nephrotic syndrome, and systemic lupus erythematosus may additionally cause protein loss from the GI tract without any discernible

mucosal lesions in the bowel [1]. PLE should be considered in patients with hypoalbuminemia and edema in whom other possible causes as stated above have been excluded. To detect GI protein loss, fecal clearance of alpha 1-antitrypsin is commonly used, however studies have increasingly used ^{99m}Tc-HSA to image PLE since its introduction in 1986 [2, 3].

CASE REPORT

A nine-month old male baby presented with complaints of facial puffiness, occasional cough and

fever since 2 months. Facial puffiness was non – progressive, more in the morning which subsides by evening. It was not associated with abdominal pain or distension. Fever was low grade, not associated with chills or rigors, and was relieved with antipyretics. Loose watery stools did not foul smell, and occurred 8-10 times a day. There was no blood or mucus in stools. During this time period his facial puffiness worsened and persisted almost through out the day. Baby was started on higher antibiotics (ofloxacin) and his diarrhea subsided after 3-4 days.

Apparently baby was normal for 1 week when he developed recurrence of loose stools 5-6 times per day. On close interrogation, parents revealed that baby started having spells of intermittent diarrhea from the age of 3.5 months.

The laboratory tests revealed hypoproteinemia (both albumin and globulin) and iron deficiency anemia. Differential diagnosis entertained were Nephrotic syndrome, Cystic fibrosis (in view of recurrent diarrhea and respiratory complaints), Chronic liver disease (in view of firm palpable liver, and lastly PLE. Urine routine examination was negative for proteins; Urine protein creatinine ratio and 24 hours urine protein were also negative. Liver enzymes and sweat analysis for cystic fibrosis were normal.

To explain PLE in our patient, primary lymphangiectasia, secondary to Celiac disease, intestinal parasitosis or difficile infection, and inflammatory bowel disease were considered. Stool for presence of fat was normal, tissue transglutaminase IgA Antibody was within normal limits. IgA, IgG, IgM values and were found to be normal. Antigliadin antibody was negative. The loss of protein into the gut was confirmed by fecal clearance of alpha -1 antitrypsin which was elevated

(108 mg/Dl). Blood and urine cultures were negative. USG abdomen and chest x ray was also unremarkable. While ruling out all the possible causes of PLE, iron deficiency anemia was implicated in our patient which was substantiated by the fact that his elevated fecal alpha 1 antitrypsin levels returned to normal after correction of iron deficiency anemia.

With the non- availability of most of the documented radiotracers for PLE in developing countries, ^{99m}Tc -MDP abdominal scintigraphy is a useful alternate based on its albumin binding properties (30% of injected MDP binds to plasma proteins). Abdominal planar scintigraphy was performed to assess and localize protein loss through gut at multiple time intervals after the intravenous injection of 111 MBq ^{99m}Tc -MDP after quality control approval.

Initial dynamic and soft tissue phase images of abdomen were normal. 3 hour delayed images showed abnormal ^{99m}Tc -MDP in right lower abdominopelvic region which was equal to the uptake in iliac bone suggestive of moderate protein loss from intestinal loops (SPECT CT facility was not available at that time) (Figure 1).

No tracer activity was noted in the thyroid, stomach and salivary glands ruling out presence of free pertechnetate. Baby was treated with a high protein diet and his iron deficiency was corrected, his loose stools subsided, and facial puffiness decreased. His serum albumin increased spontaneously. A paediatric gastromedicine consultation was also taken and patient was advised symptomatic conservative management in view of spontaneous improvement in serum albumin.

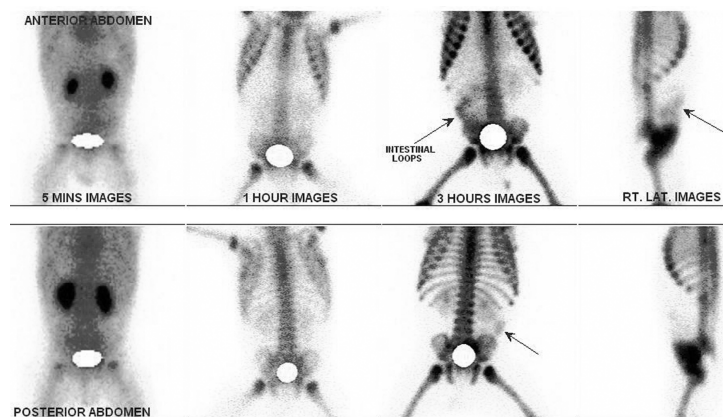


Fig 1. ^{99m}Tc MDP abdominal scintigraphy - Initial dynamic and soft tissue phase images of abdomen were normal. Delayed images showed abnormal ^{99m}Tc MDP in right lower abdominopelvic region (depicted by an arrow) which was equal to the uptake in iliac bone suggestive of moderate amount of GI protein loss.

DISCUSSION

Most of the radiotracers used in the detection of protein loss have many limitations, such as rapid re-absorption of the radiolabel [4], unstable protein binding both in vivo and in vitro, and limited availability [4-6]. The need for measurement of fecal radioactivity over 3–4 days has also been a major drawback in diagnosing PLE. Active bleeding in the gastrointestinal tract may be an important cause of false-positive ^{99m}Tc -HSA scintigrams. The mechanism of intestinal tracer uptake in PLE is still unclear [5, 6] and various postulated mechanisms are (a) the increased permeability of capillary walls, which leads to exudation of plasma, or (b) local lymphatic obstruction and stasis secondary to granulomatous inflammation and fibrous tissue formation. So tracer exudation into bowel loops at the site of protein loss may be apparent due to the one or more of the above explanations [4-7].

Ergun et al [8] reviewed 2144 consecutive patients who underwent bone scan for various indications. They analyzed the results for the presence of intestinal ^{99m}Tc -MDP uptake. The intensity of MDP extravasations into intestinal loops were further grouped according to the localization and intensity (mild uptake: lower than iliac bone; moderate uptake: equal to iliac bone; significant uptake: higher than iliac bone). They reported that 1 % of bone scans showed intestinal MDP uptake [8]. Delayed imaging, additional spot views and SPECT studies help in the differentiation of this finding from possible misinterpretation [8]. PLE may be caused by a diverse group of malignant and non malignant diseases such as gastric carcinoma, ulcerative colitis, regional enteritis, Whipple's disease, tropical and non-tropical sprue, and giant hypertrophy of the gastric mucosa [8]. Numerous radiotracers like ^{131}I / ^{125}I polyvinylpyrrolidone, ^{51}Cr Chromium labelled albumin/chromic chloride, ^{125}I -albumin, ^{111}In indium chloride /transferrin, ^{99m}Tc -DTPA, ^{99m}Tc -HSA, ^{99m}Tc -dextran, and ^{99m}Tc -human immunoglobulin have been used with variable success [9-11].

Although ^{99m}Tc is an ideal tracer for imaging of PLE, it does not allow quantification of protein loss due to its short physical half-life. On the other hand, ^{99m}Tc agents cannot cross intestinal mucosa because of the impermeable barrier between the vascular endothelium and luminal contents. They therefore remain in the vascular compartment with a long intravascular half-life [1] which is helpful in localising the site of GI protein loss. Hence, sites of protein loss may also be demonstrated within the 24-hour imaging period.

^{99m}Tc -HSA is an established tracer for this indication as there is no need for additional patient preparation

prior to undertaking the test apart from excellent in vivo stability of tracer, no serious side effects and a high sensitivity. The other advantages being cost effectiveness, rapid results, wide availability, and chance to monitor entire gastrointestinal tract continuously over several hours (24 hour imaging can increase the detection rate for PLE in the background of slow, intermittent protein loss). Disadvantages of agents like ^{99m}Tc -dextran and ^{99m}Tc -human immunoglobulin are they cannot easily differentiate PLE from localized bowel loop inflammation [12]. However ^{99m}Tc is preferred over ^{111}In agents due to its wider availability, lower radiation exposure and simplicity. ^{99m}Tc -dextran [12, 13], however, can occasionally produce an anaphylactic reaction. Also, a variety of adverse reactions, albeit uncommon, have been reported with ^{99m}Tc -HSA, including nausea, vomiting, erythema, flushing, hypotension, dyspnea, tachycardia, dizziness, and abdominal pain [14]. HSA kit is composed of 5 mg of albumin and MDP cold kit is made up of 10 mg of MDP (30% of IV MDP binds to plasma proteins). No such adverse effects are noted with MDP, however delayed images can mask the subtle tracer extravasations as a result of PLE due to background bone localization.

When introduced intravenously MDP leaves the bloodstream with a pharmacokinetics characterized by a three compartment model. During the initial, rapid phase, ^{99m}Tc -MDP is excreted to the extravascular space. The medium phase corresponds to bone uptake while the slow phase depicts the dissociation of ^{99m}Tc -MDP bound to plasma proteins in blood which is evident in PLE 2-3 hours post injection. Maximum bone uptake is attained 2 hour post-injection. Tracer clearance occurs via the urinary route. Usually the tracer activity observed in the liver and intestinal loops is insignificant in a normal bone scan, making it an agent of choice for identifying intestinal protein loss. Intestinal ^{99m}Tc -MDP uptake on bone scan could be an intermittent process and should be included among other well-known reasons of soft-tissue uptake.

According to the American Gastroenterological Association (AGA), among people with iron deficiency and no gastrointestinal symptoms of celiac disease, 2% to 5% will have positive blood parameters for celiac disease. Of them 3- 9% will have positive biopsies [15]. In patients with iron-deficiency anemia who do have GI symptoms, the prevalence of celiac disease is even higher: 10% to 15% [15]. Therefore, the AGA recommends that patients with unexplained iron-deficiency anemia be investigated for the presence of celiac disease as was done for our patient. GI protein loss may be secondary to iron-deficiency anemia among celiacs and may result due to intake of gluten which

produces an intense inflammatory response in their intestinal loops. Treatment of PLE includes targeting the underlying disease, dietary modification, supportive care, and maintenance of nutritional status. The prognosis of PLE is unknown and mainly depends upon the identification of underlying disease.

CONCLUSION

Alpha-1 antitrypsin clearance and scintigraphic techniques are useful tools to measure GI protein loss and localize the site of intestinal protein leak. Disorders that lead to PLE can be identified by thorough clinical history, laboratory tests, and imaging studies. Our case highlights the simplicity of scintigraphic techniques in establishing the diagnosis of PLE in routine clinical practice. Although MDP is not ideal due to background activity in bones, it may be useful in the event of non availability of better tracers like ^{99m}Tc -HSA.

REFERENCES

- Halaby H, Bakheet SM, Shabib S, Powe JE, Al Mehaidib A, Nazer H. ^{99m}Tc -human serum albumin scans in children with protein-losing enteropathy. *J Nucl Med*. 2000 Feb;41(2):215-9.
- Divgi CR, Lisann NM, Yeh SD, Benua RS. Technetium-99m albumin scintigraphy in the diagnosis of protein-losing enteropathy. *J Nucl Med*. 1986 Nov;27(11):1710-2.
- Florent C, Vidon N, Flourié B, Carmantrand A, Zerhani A, Maurel M, Bernier JJ. Gastric clearance of alpha-1-antitrypsin under cimetidine perfusion. New test to detect protein-losing gastropathy? *Dig Dis Sci*. 1986 Jan;31(1):12-5.
- Freeman T, Gordon AH. Measurement of albumin leak into the gastrointestinal tract using I-131 albumin and ion exchange resins by mouth. *Gut*. 1964 Apr;5:155-7.
- Martinez-Sanchis B, Cortés-Vizcaino V, Frontado-Morales L, Sopena-Novales P. Intestinal uptake of (^{99m}Tc)-MDP: a case report of protein-losing enteropathy correlated with pathology findings from autopsy. *Ann Nucl Med*. 2011 Feb;25(2):139-41.
- Seok JW, Kim S, Lee SH, Kim IJ, Kim YK. Protein-losing enteropathy detected on Tc-99m HSA and Tc-99m MDP scintigraphy. *Clin Nucl Med*. 2002 Jun;27(6):431-3.
- Uzuner O, Ziessman HA. Protein-losing enteropathy detected by Tc-99m-MDP abdominal scintigraphy. *Pediatr Radiol*. 2008 Oct;38(10):1122-4.
- Ergün EL, Kiratlı PO, Günay EC, Erbaş B. A report on the incidence of intestinal ^{99m}Tc -methylene diphosphonate uptake of bone scans and a review of the literature. *Nucl Med Commun*. 2006 Nov;27(11):877-85.
- Meristoudis G, Birbilis C, Ilias I, Tsaroucha A, Batsakis C, Christakopoulou J. Intestinal accumulation of ^{99m}Tc -MDP in a patient with protein-losing enteropathy. *Eur J Nucl Med Mol Imaging*. 2008 Jan;35(1):224.
- Waldmann TA. Gastrointestinal protein loss demonstrated by Cr-51-labelled albumin. *Lancet*. 1961 Jul 15;2(7194):121-3.
- Plantin LO, Strandberg O. Gastrointestinal protein loss in rheumatoid arthritis, studied with ^{51}Cr -chromic chloride and ^{125}I albumin. *Scand J Rheumatol*. 1974;3(4):169-73.
- Bhatnagar A, Mishra P, Singh AK, Taneja V, Chauhan UP, Sawroop K. Scintiscan demonstration of localized bowel loop inflammation. Comparison of Tc-99m dextran, Tc-99m citrate, and Tc-99m human immunoglobulin G. *Clin Nucl Med*. 1996 Sep;21(9):685-8.
- Bhatnagar A, Singh AK, Lahoti D, Singh T, Khanna CM. Technetium-99m dextran: a promising new protein-losing enteropathy imaging agent. *Eur J Nucl Med*. 1996 May;23(5):575-8.
- Silberstein EB, Ryan J. Prevalence of adverse reactions in nuclear medicine. Pharmacopeia Committee of the Society of Nuclear Medicine. *J Nucl Med*. 1996 Jan;37(1):185-92. [Erratum: *J Nucl Med* 1996 Jun;37(6):1064-7.]
- AGA Institute. AGA Institute Medical Position Statement on the Diagnosis and Management of Celiac Disease. *Gastroenterology*. 2006 Dec;131(6):1977-80.