

^{99m}Tc HSA Scintigraphy; Intestinal Protein Loss in Scrub Typhus

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^{99m}Tc-HSA 신티그램을 이용한 쯤쯤가무시병에서의 장내단백소실 진단

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Scrub typhus의 발현증상에는 저알부민혈증, 단백뇨, 전신 부종 등을 들 수 있다. 그러나, 저알부민혈증에 비해 단백뇨와 부종 등은 심하지 않은 경우가 많다. 본 연구에서는 저알부민혈증이 장내에서의 단백질 소실에 의한 것인지를 확인하고자 하였다.

Scrub typhus가 의심되는 25명의 환자를 대상으로 (1) 저알부민혈증의 원인 장내 단백질 소실에 의한 것인지 여부와 (2) ^{99m}Tc-HSA 신티그램의 진단적 유용성을 알아보려고 하였다. 신티그램은 혈청학적 검사상 Scrub typhus로 확인된 18명의 환자에서 (13예는 항생제 치료 개시후 1일에서 8일 사이에, 5예는 치료 전에 시행하였으며, 11예에서는 대변에서 alpha-1- antitrypsin (α AT)배설 여부를 확인하였다.

촬영방법은 ^{99m}Tc-HSA 30mCi를 정맥 주사한 후, 2, 4, 6, 24시간에 복부 전면상을 얻었다. 판정은 소장과 대장의 주행 위치에서의 혈관의 방사능 소견을 장내 단백질 소실로 간주하였다.

13예에서 양성으로 판정하였는데, 이중 8예는 대변에서의 α AT치도 높게 나왔다. 신티그램상 음성을 보인 5예중 2예에서는 대변중 α AT치가 매우 높게 나왔는데 그 이유는 신티그램 검사는 치료 도중에 하였고, 대변 검사는 치료 전에 하였기 때문인 것으로 간주하였다. 결론적으로 전체 18예중 15예에서 신티그램이나 대변검사로 Scrub typhus로 진단하였다.

한편, 13예 (72%)에서 저알부민혈증을 보였는데 이중 4예는 장내단백질 소실과 단백뇨를, 5예는 장내단백질 소실만을, 3예에서는 단백뇨만을 보였고, 1예는 아무 소견이 없었다.

요약하면, 장내단백질 소실 소견은 Scrub typhus환자의 83%에서 보여, 혈중 알부민치가 저하되는 원인으로 추정된다. 따라서 ^{99m}Tc-HSA 신티그램은 장내단백질 소실의 진단에 매우 유용한 검사방법이다. 또한, 검사방법이 다소 어렵지만 대변에서의 α AT측정도 동위원소 검사상 음성 소견을 보이는 환자에게는 어느 정도 진단에 도움을 주리라 보여진다.

Key Words : Intestinal Protein Loss, Scrub Typhus

INTRODUCTION

Hypoproteinemia may result from a variety of conditions including deficient protein intake, congenital hypoalbuminemia, liver disease, or

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excessive protein loss. Excessive loss of protein may be caused by nephrotic syndrome or intestinal loss of protein. Intestinal loss of protein (ILP) has been reported in ulcerative colitis, Crohn's disease, cirrhosis and in some vascular diseases such as systemic lupus erythematosus or Henoch-Schönlein purpura^{14, 15, 19}.

Scrub typhus, an infectious disease by *R. tsutsugamushi*, is common in Asia and Pacific area including Korea. Its basic pathology is systemic vasculitis involving the kidney, liver and skin. Hypoalbuminemia has been reported in 8-38% of the patients in Korea, and it may be thought to result from proteinuria or impaired hepatic synthesis. We observed hypoalbuminemia in some patients without or, if any, mild proteinuria or hepatic impairment.

Another possible cause of hypoalbuminemia in this group may be ILP, but there was no document about the ILP or vasculitis of the intestinal tract resulting in leak of protein.

ILP has been quantified by measurement of fecal excretion of albumin radiolabelled with ^{131}I or ^{51}Cr ^{5, 7, 21}, and by measurement of fecal excretion of alpha-1-antitrypsin (αAT)^{1, 5, 8, 10, 18}. These methods need stool collection and are cumbersome. Recently scintigraphic imaging was introduced for diagnosis of ILP^{6, 17}.

We prospectively performed ^{99m}Tc -human serum albumin (HSA) abdominal imaging in 25 patients suspected having scrub typhus to test 1) if there is ILP in the disease and 2) to test the usefulness of the method by comparison with measurement of fecal excretion of αAT .

MATERIALS AND METHODS

1. Patients

From October to November 1994, 24 patients were collected at Kangnam St. Mary's Hospital in Seoul and Ujongbu St. Mary's Hospital near

the demilitarized zone in Korea. All of the patient information was summarized in Table 1.

^{99m}Tc -HSA abdominal imaging was prospectively in 24 patients suspected of having scrub typhus, and scrub typhus was serologically proven in 18 patients. Remaining six patients were dropped in this study. Among these six patients, one patient was confirmed as having murine typhus, and remaining five patients were clinically diagnosed as having scrub typhus but it was not proved serologically.

Of 18 patients, 13 had scans 1 to 8 days after an antibiotic treatment was started and five patients had scans before the treatment.

Fecal excretion of αAT was measured in 11 of 18 patients before the antibiotic treatment. Laboratory tests included serological test for scrub typhus, routine complete blood count, blood chemistry and urinalysis. Occult blood in stool was also tested.

2. Scintigraphy

Scintigraphy was performed by gamma camera (Orbiter by Siemens, Germany and Sophy by Sopha, France) in the anterior position over entire abdomen at 5 min, 2, 4 and/or 6 hours, and 24 hours. One million counts were acquired after intravenous injection of 30 mCi of ^{99m}Tc -HSA (Daiichi, Japan). Additional oblique views were obtained if needed. Extravascular activity moving along the course of small and large intestines was considered positive for ILP. Anterior neck images were also obtained at 24 hours after injection for assessment of free technetium.

3. Fecal αAT Excretion

A 5g aliquot of feces was obtained at the time of the admission, frozen and stored at -20°C . It was lyophilized for 16 hours and then ground into a fine powder with a mortar and pestle. A 250 mg of the powder was added into 5 ml of normal saline at room temperature and

Table 1. Twenty-five Patients Studied

No.	Age	Sex	Scan	Scan-treatment interval (days)	α AT	Proteinuria	Albumin (g/dl*)	Abdominal Sx	Sx duration (days)	Scrub typhus Ab titer	Occult blood
1	58	F	+	8	+	++	2.4	+	11	+	
2	53	F	+	6	+	++	3.1	-	9	+	
3	27	F	+	2	+	++++	3.1	-	2	+	
4	47	F	+	1	NA	+++	2.7	-	1	+	
5	46	F	+	3	NA	+++	2.8	-	7	+	+
6	65	F	+	2	NA	-	3.0	+	7	+	
7	73	F	+	9	NA	+	2.9	+	3	-	
8	46	M	-	11	NA	-	3.6	-	5	MT	
9	49	F	-	2	+	+	3.1	-	6	+	
10	77	F	-	5	NA	++	2.5	+	5	+	
11	60	M	-	5	NA	+	3.1	-	14	+	
12	72	F	-	5	-	+	2.5	-	13	-	
13	25	F	-	0	NA	+	3.1	+	3	-	
14	34	M	+	0	NA	-	3.0	+	6	+	
15	36	F	+	4	+	++	2.6	+	14	+	
16	25	F	+	1	NA	+	3.4	-	6	-	
17	23	M	+	3	NA	+++	3.5	-	14	+	
18	26	F	+	0	NA	-	3.3	+	7	-	
19	60	F	+	0	+	-	2.8	+	9	+	
20	46	F	+	0	+	-	3.9	-	3	+	
21	65	F	+	0	+	-	3.3	+	10	+	
22	58	F	-	5	+	-	3.6	-	10	+	
23	68	F	-	0	-	-	3.4	+	5	+	++
24	45	M	+	2	+	-	3.9	+	5	+	
25	64	M	+	2	+	-	2.8	-	5	+	

α AT : alpha-1-antitrypsin stool, NA : not available, MT : murine typhus, Sx : symptom
 *albumin : by BCG method, 3.5-5.5 g/dl

mixed vigorously with vortex apparatus for 30 minutes, then centrifuged at 4,200 g for 15 minutes at 4°C. Five μ l of aliquot of supernatant was then taken and α AT was measured using nephelometer (Samofi, QM 300, USA). Normal range of α AT was 0.56 ± 0.35 mg/g dry weight of stool and α AT excretion more than 1.136 mg/g dry weight (mean ± 1.645 SD) was considered positive.

4. Serological Study of R. Tsutsugamushi

Blood samples were obtained at the time of

the admission and if negative, two to three times at 3-4 days intervals. Antibody titers of Gilliam, Karp and Kato stains were tested by indirect immunofluorescent method. Increased titer four times higher than the standard was considered positive.

RESULTS

Symptoms and signs included acute onset of fever, eschar, rash, nausea, vomiting, abdominal

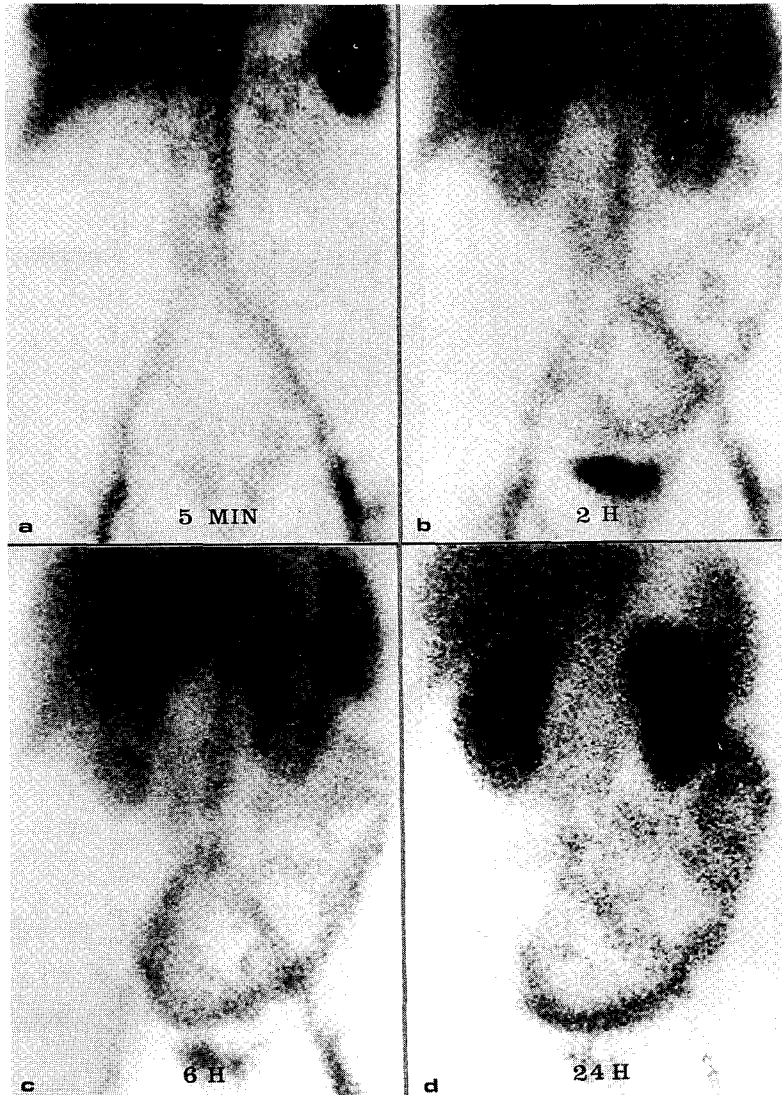


Fig. 1. (a-d). Positive scintigraphy. Definite intestinal activity is noted in the lower abdomen from 2 hours after injection of ^{99m}Tc -HSA. The stomach does not show significant tracer uptake.

pain, diarrhea, myalgia, multiple joint pain, and generalized edema. All the patients had history of outdoor activities such as cramping, picnic, or working in the fields. Symptom duration varied from one to 14 days with mean of 7.8 days.

Of 18 patients with scrub typhus (Fig. 1, 2), 13 had positive scan. None of the patients with positive scan showed thyroid or significant

gastric uptake. Among these 13 patients, scans were performed before the antibiotic treatment in three patients and after in ten patients. Fecal α AT was measured in eight of these 13 patients, all of which were also positive for ILP. Among five patients with negative scans, α AT was measured in three patients and two of the three patients showed excessive fecal α AT excretion

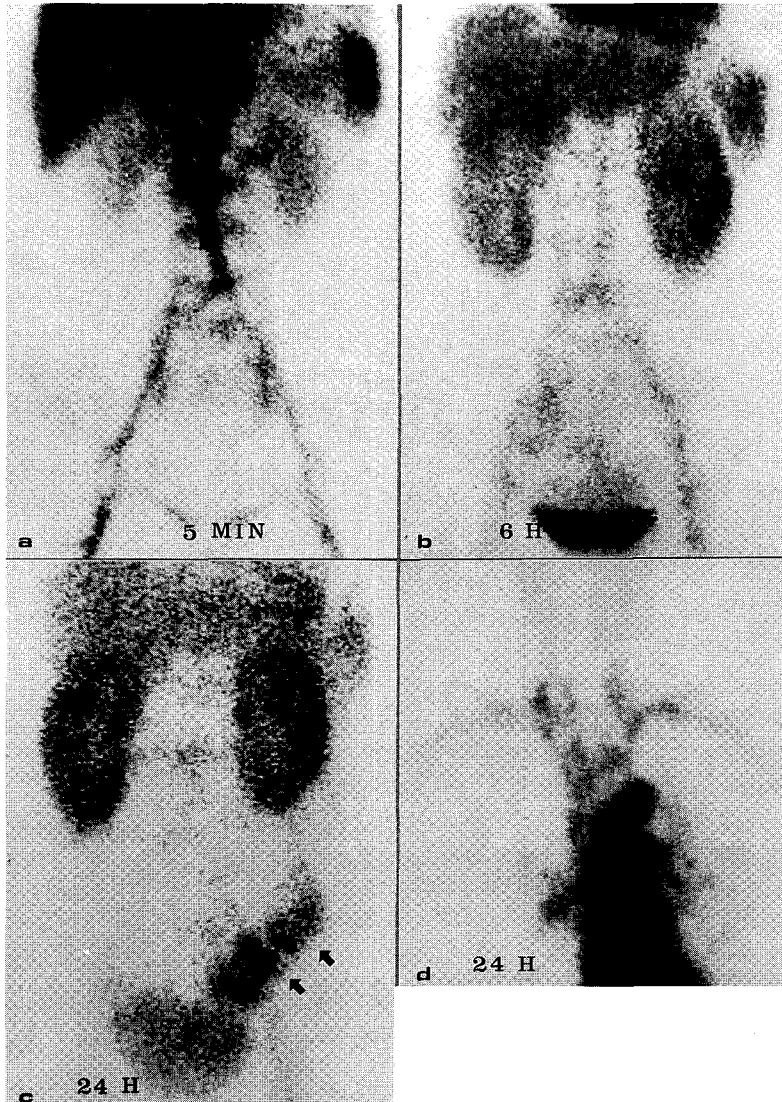


Fig. 2. (a-d). Positive scintigraphy. There is no definite intestinal activity until 6 hours (a-b), but colon activity (arrows) is shown on 24 hour-delayed scan (c). Thyroid uptake is not noted at 24 hours (d).

Table 1. Alpha-1-antitrypsin (α AT) vs Scintigraphy in 11 of 18 Patients with Scrub Typhus

		^{99m}Tc -HSA scan	
		positive	negative
α AT	positive	8	2
	negative	0	1

Sensitivity 80%, Specificity 100%

(Table 2).

At any rate, of the total 18 patients with scrub typhus in this study, 15 patients (83%) showed evidence of ILP by either scintigraphy or fecal α AT, or both. 13 of the 18 patients (72%) had hypoalbuminemia. Of these 13 patients, four had ILP and proteinuria, five had ILP only, three had

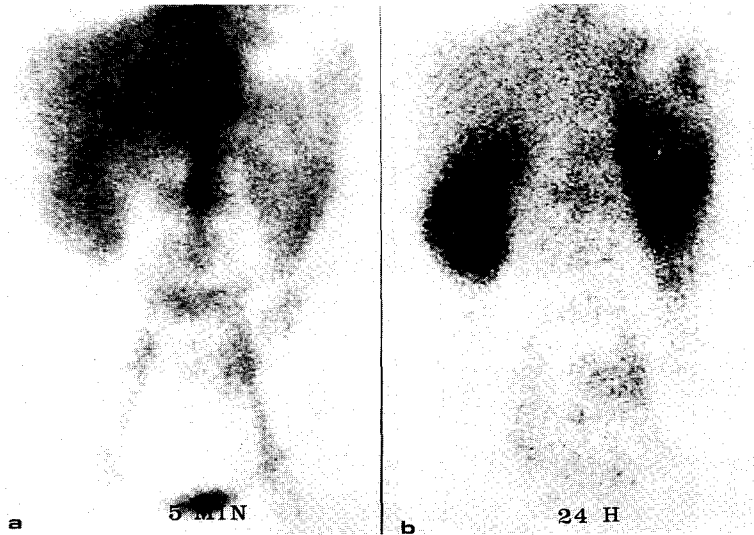


Fig. 3. (a, b). Negative scintigraphy. No definite intestinal activity is seen till the end of the study.

proteinuria only, and one had neither. Intestinal loss of protein was identified even in four of the five patients with a normal serum albumin (two of the four also had proteinuria). The remaining one had neither (Fig. 3). Among 18 patients with scrub typhus, two had occult blood in stool (patient No. 5 and 23). One showed positive and the other negative scintigraphy.

In this series, ILP was present in 83% of patients with scrub typhus, which was substantially higher than expected. Four patients with normal plasma albumin had also showed ILP.

DISCUSSION

Scrub typhus is an infectious disease caused by *R. tsutsugamushi*, which is endemic in Asia and Pacific areas including Korea. It is characterized by acute onset of fever, chill, headache, lymphadenopathy, and sometimes generalized ache or myalgia, eschar, and rash²⁾. Some patients have hepatosplenomegaly, abdominal pain, nausea, vomiting and diarrhea. With careful clinical history and physical examination it is not so

difficult to make a diagnosis in the epidemic area.

A basic pathology of rickettsial disease such as Rocky mountain spotted fever, murine typhus and scrub typhus is systemic vasculitis¹⁶⁾. Rickettsiae apparently have affinity for and proliferate in the endothelial cells of small blood vessels. Spont destruction of these cells occurs from the proliferation of organisms and eventual disruption. Rickettsiae may exert a cytotoxic effect on endothelial cells in mice and toxin cause remarkable increase in capillary permeability resulting in leak of water, electrolytes, proteins and erythrocytes. These changes are noted in multiple organs including the kidney, lung, heart, liver, muscle, serosal surfaces and skin. To our knowledge, however, there was no document about a pathologic changes secondary to vasculitis in the bowel or mucosal surface. Some gastrointestinal symptoms such as diarrhea, abdominal pain, nausea and vomiting were reported in 10-70 % of the patients with scrub typhus in Korea^{3, 4, 11, 12, 13)} and these symptoms may be due to intestinal involvement of the

disease. Moreover, epistaxis is reported in 11 % of the patients probably suggesting the mucosal involvement of the disease¹¹⁾.

We found hypoalbuminemia in the patients with scrub typhus and it has been reported in 8-38 % of the patients in Korea. It was observed even in the patients without or with mild proteinuria or hepatopathy, and we postulated that the ILP might be another possible cause of hypoalbuminemia.

Intestinal loss of protein has been diagnosed by a measurement of fecal excretion of albumin labeled with ¹²⁵I or ⁵¹Cr, and ¹²⁵I-polyvinyl pyrrolidone¹⁹⁾ after intravenous injection of the tracers, but it needs collection of stool. Recently measurement of fecal excretion of α AT has become commonly used for the detection of ILP, but is also cumbersome and needs stool collection. ^{99m}Tc-HSA abdominal imaging was used for the diagnosis of ILP by Divgi et al (1986) and unexpected ILP has been imaged in the patients with collagen disease such as systemic lupus erythematosus, Hennoch-Schönlein purpura or lymphangiectasis¹⁷⁾. We tested if there is ILP in the patients with scrub typhus using ^{99m}Tc-HSA abdominal scintigraphy and the measurement of fecal excretion of α AT.

Scintigraphy was positive in 13 of 18 patients with scrub typhus. ILP was confirmed by fecal α AT in eight of 13 patients. Two of six patients with negative scintigraphy showed excessive fecal α AT. These patients took scintigraphy two and five days after beginning of antibiotics and patients were considered having ILP treated by antibiotics.

It is known that chloramphenicol or tetracycline antibiotics are extremely effective in scrub typhus and the patients regularly afebrile and are decidedly improved within 24 to 36 hours after beginning of the treatment irrespective of the stage of the disease. As compared with fecal α

AT, sensitivity and specificity of scintigraphy were 80% and 100%, respectively (Table 2).

Two patients had occult blood in stool. Patient No.5 had trace occult blood and positive scan while patient No.23 showed (++) occult blood but negative on scintigraphy. We cannot explain the cause of the discrepancy, but postulate that ^{99m}Tc-HSA may not be sensitive enough to detect small amount of intestinal bleeding.

So at any rate, 15 of 18 patients (83%) with scrub typhus showed ILP in this study. Plasma albumin level was low in 13 patients (72%) and normal in 5 patients. Among 13 hypoalbuminemic patients 4 had proteinuria and ILP, 5 had ILP only and 3 had proteinuria only. Four of 5 patients with normal plasma albumin also showed ILP and 2 of them had proteinuria too. This may suggest that the intestinal involvement is as common as hepatic and renal involvement of the disease. In this study nine of 18 patients had symptoms and signs such as abdominal pain, diarrhea and occult blood in stool, which may be due to intestinal involvement supporting our data.

ILP might not be clinically significant in the scrub typhus because the prognosis of the disease is good and it can be easily treated, but we think ILP might be higher than expected in many conditions with hypoalbuminemia of unknown origin and its diagnosis may be critical in some diseases for the patient care. ^{99m}Tc-HSA scintigraphy can be used as a screening test in the patients with hypoalbuminemia of unknown origin.

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