Intractable diarrhoea associated with secondary amyloidosis in rheumatoid arthritis

Yasuki Okuda, Kiyoshi Takasugi, Tetsu Oyama, Hiroko Oyama, Shigeru Nanba, Takeshi Miyamoto

Abstract

Objective—To examine the clinical characteristics of intractable diarrhoea associated with secondary amyloidosis in rheumatoid arthritis (RA).

Methods—Of 179 RA patients with biopsy confirmed secondary amyloidosis, 24 cases (23 women and one man) with intractable diarrhoea lasting for more than one month were retrospectively evaluated.

Results—The mean (SD) duration of diarrhoea was 87 (64) days. Prodromal symptoms of gastrointestinal dysfunction (n = 21) and impaired peristalsis (n = 16) were observed. Laboratory data showed hypoproteinaemia (4.7 (0.85) g/dl) caused by malabsorption or protein loss and high values of C reactive protein (17.0 (9.3) mg/dl). Recurrence of intractable diarrhoea (n = 4) and transition from intractable diarrhoea to other gastrointestinal problems of amyloidosis (ischaemic colitis (n = 2) and intestinal pseudo-obstruction (n = 4)) were observed. In 19 patients (25 episodes) the duration of intravenous hyperalimentation at remission (18 episodes) was 68 (52) days. Corticosteroid pulse therapy was administered to 10 patients (11 times) and the time elapsed from the end of corticosteroid pulse therapy to the end of diarrhoea was 18 (14) days. One and five year survival rates after the onset of intractable diarrhoea were 73.4% and 38.9%. Seven of 13 patients (54%) had died as a result of infectious diseases.

Conclusion—Intractable diarrhoea associated with secondary amyloidosis in RA is a serious clinical entity and the prognosis is poor. Although it is assumed that intravenous hyperalimentation treatment and corticosteroid pulse therapy are favourable regimens for intractable diarrhoea, the patients should be monitored for possible infectious complications.

Secondary amyloidosis is a disease characterised by extracellular deposition of amyloid A protein, which is the result of excessive generation and abnormal degradation of serum amyloid A (SAA).

Recent clinical studies have shown that the prevalence of amyloidosis proved by biopsy in rheumatoid arthritis (RA) patients is about 10%. Among the complications of RA, secondary amyloidosis is one of the most severe complications in the late stages of RA because of its poor prognosis.

Secondary amyloidosis commonly affects the gastrointestinal tract as well as the kidneys, as shown by various clinical symptoms that include anorexia, nausea, vomiting, feeling of abdominal fullness, abdominal pain, diarrhoea, melana, and perforation of the gastrointestinal tract. In particular prolonged intractable diarrhoea is severe, distressing, and often unresponsive to treatment. Thus, it is essential to clarify the clinical characteristics, the treatment, and the prognosis of intractable diarrhoea associated with secondary amyloidosis in patients with RA. While case reports have been reported, we believe this is the first attempt to describe a retrospective series in a defined population with secondary amyloidosis caused by RA. In this case record review, clinical features and prognosis are examined.

Methods

Patient Selection

The inclusion criteria for this retrospective study were as follows: RA diagnosed according to the criteria for the classification of RA of the American College of Rheumatology (formerly the American Rheumatism Association) of 1987, and the presence of intractable diarrhoea. Intractable diarrhoea was defined as sustained watery diarrhoea that did not respond to treatment with the antidiarrhoeal drugs such as albumin tannate, berberine, loperamide hydrochloride for more than one month and having no other cause of diarrhoea than secondary amyloidosis, such as bacterial enterocolitis or pancreatic diseases. The termination of diarrhoea was defined when a formed stool was observed.

For the patients who survived, the mean (SD) time from the diagnosis of amyloidosis to the final assessment was 1606 (1172) days (median 1681, 102–3260), and the mean (SD) time from the onset of intractable diarrhoea to the final assessment was 1494 (1221) days (median 1684, 56–3312)

Study Design

Tissue staining with Congo red and antiserum against amyloid A protein were routinely performed to establish the diagnosis of secondary amyloidosis.

All the patients with intractable diarrhoea had deposits of amyloid A protein on the gastrointestinal tract mucosa (stomach, duodenum or colon). When specimens confirmed positive staining for amyloid deposits on gastrointestinal tracts, they were divided...
Table 1  Clinical features in 24 patients with rheumatoid arthritis and intractable diarrhoea caused by secondary amyloidosis

<table>
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<tr>
<th>Patient</th>
<th>Age/sex</th>
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<th>Nadir Alb (g/dl)</th>
<th>Max CRP (mg/dl)</th>
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TP=total protein; Alb=albumin; CRP=C reactive protein. *Age at diagnosis of amyloidosis; †Nadir values during the course of intractable diarrhoea. **Maximum values during the course of intractable diarrhoea.
Intractable diarrhoea associated with secondary amyloidosis in rheumatoid arthritis

Table 3 Endoscopic findings in rheumatoid arthritis patients during intractable diarrhoea caused by secondary amyloidosis

<table>
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<tr>
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CMA = coarse mucosal appearance; ER = erosion; UL = ulcer; RED = redness; BL = bleeding; NA = no abnormality; rec = rectum; sig = sigmoid colon; des = descending colon.

Table 3 summarises the main RA features of the 24 cases. Only one case showed the creatinine concentration in excess of 1.0 mg/dl at the onset of intractable diarrhoea. Minor proteinuria (<1 g/24h) was seen in four cases. None of the cases showed heart failure, low voltage electrocardiogram or hypothyroidism. Many cases showed increased Lansbury activity indices and C reactive protein values. Prodromal symptoms of gastrointestinal dysfunction were observed in 21 cases (88%), and the symptoms were repeatedly observed from one year or several months before the onset of intractable diarrhoea.

Other possible causes of the induction of intractable diarrhoea were recognised in six cases including three cases of infection, two cases of operation, and one case of extraarticular manifestation (myocarditis). The three episodes of infection were purulent arthritis of left knee, meningitis caused by candida albicans, and hepatitis caused by cytomegalovirus. The two cases of intractable diarrhoea caused by operation started to manifest intractable diarrhoea 14 days after the synovectomy of bilateral knees and 24 days after the fusion of cervical spine, respectively. Greatly increased C reactive protein values were observed in all six cases before the onset of intractable diarrhoea (median; 14.4 mg/dl, range; 6.3–22.5 mg/dl).

The abdominal features during the course of intractable diarrhoea included pain in 22 cases (92%), nausea in 21 (88%), vomiting in 20 (83%), and distension in 16 (67%).

Table 2 summarises the clinical findings and the laboratory data of the 24 cases. The duration of diarrhoea was 87 (64) days (median 150, range 32–268) and the frequency of diarrhoea was 7 (3) times/day (median 10 times/day, range 4–16 times/day). The nadir total protein concentration and the nadir albumin concentration during the course of diarrhoea were 4.7 (0.85) g/dl (median 4.6 g/dl, range 3.0–6.2 g/dl) and 2.2 (0.43) g/dl (median 2.2 g/dl, range 1.3–3.1 g/dl), respectively. The maximum C reactive protein value during the course of intractable diarrhoea was very high (17.0 (9.3) mg/dl; median 22.9 mg/dl, 6.3–39.5 mg/dl).

Table 3 summarises the endoscopic findings of 16 cases in which upper gastrointestinal or colon endoscopy was performed during the course of intractable diarrhoea. Abnormal findings were observed in the stomach or duodenum or colon in all the cases. Coarse mucosal appearance such as fine granular elevation or irregular mucosa was seen in 12 cases (75%) and mucosal injuries (ulcer, erosion, bleeding or redness) were observed in 11 cases (69%) in upper gastrointestinal or colon endoscopy (figs 1 and 2). On the other hand, in the non-intractable diarrhoea patients on whom upper gastrointestinal or colon endoscopy were performed at the time of diagnosis of secondary amyloidosis, coarse mucosal appearance was seen in 21 of 121 cases (17%), and mucosal injuries were observed in 67 of 121 cases (55%).

Gastroduodenal biopsies were conducted on all 16 cases and considerable deposits of amyloid were found in gastrointestinal tissues. In the eight cases in which no endoscopy was performed during the course of intractable diarrhoea, considerable deposits of amyloid from gastrointestinal tracts had been found before the onset of intractable diarrhoea. On the other hand, in the non-intractable diarrhoea patients who were diagnosed as secondary amyloidosis by gastrointestinal biopsy considerable deposits of amyloid were observed in 63 of 121 patients (52%).

Recurrance of intractable diarrhoea after remission or other types of gastrointestinal manifestations of amyloidosis was observed in nine cases. Figure 3 shows the transition patterns. In four cases of recurrent intractable diarrhoea, six episodes occurred and the time
elapsed before the next episode was 6 (2.8) months (3–10). Ischaemic colitis after the remission of intractable diarrhoea was observed in two cases and the time elapsed from the remission of intractable diarrhoea until the onset of ischaemic colitis was 26 and 24 months, respectively. Intestinal pseudo-obstruction during the course of intractable diarrhoea was observed in four cases, among which one case showed intestinal pseudo-obstruction during the third episode of intractable diarrhoea.

Treatment regimens of intractable diarrhoea were determined by the physician responsible for care. However, for the cases with frequent watery diarrhoea and having severe nausea and severe hypoalbuminaemia, the following treatment regimens were conducted (table 4). To allow the impaired intestine to rest and to reduce intestinal inflammation, these patients received intravenous hyperalimentation in combination with a moderate dose of corticosteroids (10 to 30 mg/day of prednisolone). For cases showing no remission of watery diarrhoea with this regimen, corticosteroid pulse therapy (100 mg × 3 days of betamethasone or 125 mg × 3 days of methylprednisolone) was administered after confirmation of absence of infectious diseases.

Intravenous hyperalimentation treatment was performed in 19 cases, 25 times, and the duration of intravenous hyperalimentation treatment of 18 episodes at the remission, excluding the deceased cases, was 6832 days (median 126, range 29–223).

The corticosteroid pulse therapy was conducted in 10 cases, 11 times. The duration of diarrhoea from its onset to the corticosteroid pulse therapy in nine cases with 10 episodes, excluding one deceased case, was 77 (76) days (median 135, range 17–253) and the duration from the end of corticosteroid pulse therapy to the end of diarrhoea was 18 (14) days (median 26.5, range 3–50).

Thirteen patients (54%) died during the study period. Table 5 summarises the causes of death. The cause of death was confirmed mainly by the clinical record. The duration from the diagnosis of amyloidosis until death and that from the onset of intractable diarrhoea until death were 843 (618) days (median 1138, range 142–2133) and 706 (728) days (median 1089, range 40–2138) respectively. Seven patients died during the course of intractable diarrhoea. One died of congestive heart failure during the third course of intractable diarrhoea. Another died because of septicaemia and one died of pneumonia after transition to intestinal pseudo-obstruction. One patient with septicaemia died after the transition to intestinal pseudo-obstruction during the course of the third episode of intractable diarrhoea.
Table 4  Treatment of intractable diarrhoea caused by secondary amyloidosis in 24 rheumatoid arthritis patients

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<tr>
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<th>CS maximum dose (mg/day)</th>
<th>CS pulse</th>
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<th>Duration of pulse (days)‡</th>
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IVH=intravenous hyperalimentation, CS=corticosteroid, M125=methylprednisolone 125 mg × 3 days, B100=beetamethasone 100 mg × 3 days, S=survival, D=death, *Maximum daily dose of prednisolone, †Duration of diarrhoea before start of corticosteroid pulse treatment, ‡Duration of diarrhoea after the end of corticosteroid pulse treatment, §Outcome of patient during the course of intractable diarrhoea. (Denotes transition from intractable diarrhoea to intestinal pseudo-obstruction before death.

SURVIVAL ANALYSIS

Figure 4 shows the overall survival curve. The percentages of patients who survived at least one, three, and five years after the onset of intractable diarrhoea were 73.4%, 57.7%, and 38.9%, respectively.

Analysis of the prognostic value of factors for survival indicated that both a high C reactive protein value (CRP ≥17 mg/dl (mean value)) during the course of intractable diarrhoea (p=0.0395) (fig 5) and intravenous hyperalimentation treatment (p=0.0484) were significantly correlated with decreased survival. Their five year survival rates were 11.8% (n = 11), versus 63.9% (n = 13) when C reactive protein was <17 mg/dl and 27.4% (n = 19), versus 75.0% (n = 5) with no intravenous hyperalimentation treatment, respectively. Hypoproteinaemia (total protein <4.7 g/dl) and short duration of arthritis at diagnosis of amyloidosis (<13 years) were associated with a trend toward decreased survival (p = 0.101 and 0.1566, respectively). But no correlation was seen between survival time and concentration of total protein (p= 0.346, p = 0.0974) or duration of arthritis at diagnosis of amyloidosis (p= 0.204, p = 0.3274). We found no significant association between decreased survival and RA features before the onset of intractable diarrhoea (Lansbury activity index, the concentration of C reactive protein, gastrointestinal symptoms , duration of diarrhoea, frequency of diarrhoea, hypoalbuminaemia, the concentration of creatinine, relapse of intractable diarrhoea or transition to other types of gastrointestinal manifestation of amyloidosis and corticosteroid pulse therapy. Although not statistically significant by log rank test (p = 0.0704), survival curves from the diagnosis of secondary amyloidosis showed lower values in the intractable diarrhoea group than in the non-intractable diarrhoea group (five year survival, 47% versus 61.1%) (fig 6).

Discussion

There is no detailed description of the clinical characteristics of patients with RA before the onset of intractable diarrhoea associated with secondary amyloidosis in previous case reports.14–17 Our present retrospective study showed that before the onset of diarrhoea, most patients showed high activity of arthritis and repeated prodromal gastrointestinal symptoms. Furthermore, some cases showed possible causes of induction of intractable diarrhoea (that is, operation, infection or extraarticular manifestation). SAA, which is the precursor of amyloid A protein, is known to be synthesised in the liver and the process is stimulated by macrophage derived cytokines such as interleukin 1, interleukin 6 or tumour necrosis factor, thus it rapidly increases in blood at the time of acute inflammation in parallel with acute phase proteins such as C reactive protein.18 It is considered that high activity of arthritis, infection, surgery and extraarticular manifestation of RA induce a rapid increase of SAA and promote the deposit of amyloid, which might contribute to the onset of intractable diarrhoea.

With regard to renal function, most patients had normal values of creatine. Even in one patient who had increased concentrations of creatine at the time of the onset of intractable diarrhoea, those values returned to normal after recovery from dehydration. It is generally assumed that intractable diarrhoea tends to manifest earlier than renal dysfunction. In fact, in 15 cases (63%) the opportunity to diagnose amyloidosis was the onset of intractable diarrhoea.
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infection, no causative bacteria such as
causes of intestinal inflammation. With regard
to clinical symptoms, abdominal pain, nausea and vomiting were seen in
almost all cases. Abdominal distension with
deleted bowel sounds on auscultation were
recognised in about two thirds of the cases,
which suggested the impaired peristalsis
resulted from amyloid deposit, \(21\) a characteris-
tic finding of gastrointestinal amyloidosis.

During the course of diarrhoea, all cases showed severe hypoproteinaemia and hypo-
albuminaemia. These results suggested malab-
sorption \(22\) or protein loss. \(24\) Moreover, highly
increased values of C reactive protein during
the clinical course were pathognomonic of
intractable diarrhoea. The increased value of C
reactive protein is assumed to be caused by
severe intestinal inflammation. And we
speculate that ischaemia of the intestinal
mucosa and gastrointestinal infection are the
causes of intestinal inflammation. With regard
to infection, no causative bacteria such as \(Shig-
ella, Salmonella, Vibrio\) or enteropathogenic
Escherichia coli were detected in faeces culture.
However, we could not perform bacteriological
examination of jejunal aspirate. And we did not
examine stool toxin of \(Clostridium difficile\)
in three cases (case 2, 16, 17) who had been given
antibiotics before the onset of intractable diar-
rhoea. Thus, it cannot be denied that change or
increase of some kind of intestinal bacterial
flora or viral infection may have triggered the
gastrointestinal inflammation.

From these clinical symptoms and abnormal
laboratory data, the impaired motility and
inflammation of the intestine are assumed to
be important pathogenic factors of intractable
diarrhoea. It is probable that amyloid
infiltration of the intestinal smooth muscle \(23\)
or gastrointestinal neuropathy with amyloid
involvement of the autonomic nerves \(22\) caused
impaired motility of the intestines.

Abnormal findings were noted in all the
patients who underwent gastrointestinal
endoscopy. The coarse mucosal appearance
reported by Tada \(23\) and Shimada \(2\) were
observed in 75% of the cases. These findings
are considered to have been caused by amyloid
deposits. Although mucosal injuries are highly
suggestive of gastrointestinal tract inflamma-
tion caused by amyloidosis we must treat these
abnormal lesions by considering the possibility
that they were induced by drugs such as
non-steroidal anti-inflammatory drugs.

Recurrence of intractable diarrhoea was
observed in four of 24 cases (six episodes) and
onset of ischaemic colitis in two. It was difficult
in most of these cases to give anti-rheumatic
drugs continuously because of the manifesta-
tion of gastrointestinal symptoms such as con-
stitipation, diarrhoea, feeling of abdominal
fullness or nausea after the remission of the
first episode of intractable diarrhoea and
adverse reactions. Therefore, these patients
sustained high RA activities, leading to the
recurrence of gastrointestinal amyloidosis. The
patients whose condition worsened and presented symptoms of intestinal pseudo-
obstruction were very serious, and three of four
cases died. The transition from diarrhoea to
intestinal pseudo-obstruction is considered as
one of the most serious conditions showing
severe gastrointestinal dysfunction.

Intractable diarrhoea was treated to allow
the impaired intestines some rest and reduce
intestinal inflammation. The patients who had
severe nausea or vomiting and those with
severe hypoproteinaemia received intravenous
hyperalimentation in combination with a mod-
erate dose of corticosteroids. Intravenous
hyperalimentation was given to suppress
exudation from digestive organs and rest the
inflamed gastrointestinal tracts. Intravenous
hyperalimentation had to be given for a
comparatively long period of time until remis-
sion, but it was effective in many cases. There
are some reports indicating the usefulness of
intravenous hyperalimentation for severe
diarrhoea caused by amyloidosis. \(15, 16\) Thus
intravenous hyperalimentation is considered an
appropriate regimen for severe cases. Patients
who did not respond to intravenous hyper-
alimentation and had diarrhoea for a long period of time, were give corti-
copteroid pulse therapy at the discretion of the
physician responsible for care. Decrease of the
frequency of diarrhoea or transition of watery
diarrhoea to soft faeces was observed early
after the end of corticosteroid pulse therapy.
Especially, in the case of patients having long
term diarrhoea (cases 11 and 12), diarrhoea
stopped on days 11 and 3 after the end of cor-
ticosteroid pulse therapy, respectively, showing
dramatic effects. Corticosteroid pulse therapy
is supposed to strongly suppress the generation
of SAS and intestinal exudation by reducing
systemic and intestinal inflammation. A
moderate dose of corticosteroids and cortico-
steroid pulse therapy are considered clinically
effective in cases of diarrhoea caused by
amyloidosis. On the other hand, however, cor-
ticosteroids are strong immunosuppressive
agents, and therefore it is important to use
them with caution for a short period of time
while paying attention to infectious complica-
tions.

As for the causes of death during the course
of intractable diarrhoea, the six of seven
patients who died, died of infectious diseases.
Bacterial translocation, that is, the transfer of
bacteria from the intestine to the whole body
was supposed to have occurred because of
malnutrition and atrophy of intestinal villi
caused by amyloid deposits and inflammation
of the gastrointestinal mucosa. In addition,
intractable diarrhoea is usually associated with
hypogammaglobulinaemia, which makes the
patients vulnerable to bacterial infections.

The most frequent cause of death during the follow-
up was renal failure (three patients). Renal fail-
ure is the main cause of death for patients with
secondary amyloidosis; thus, renal dysfunction
is a poor prognostic factor in secondary
amyloidosis. \(15, 16\) RA inflammation of the three
cases who died from renal failure was poorly controlled after remission of intractable diarrhoea and their renal function gradually deteriorated.

As for the long term prognosis, the five year survival rate of the 24 cases, from the onset of intractable diarrhoea, was as low as 38.9%. In particular, the five year survival rates of the ‘group having highly increased C reactive protein values during the course of intractable diarrhoea’ and the ‘group requiring intravenous hyperalimentation treatment’ were extremely low, 11.8% and 27.4%, respectively.

Why is the prognosis of patients with serious intractable diarrhoea so poor? There were patients who died of infectious diseases during the course of intractable diarrhoea, patients who had nausea or complained of abdominal fullness even after remission of diarrhoea, and patients who had persistent hypoproteinaemia or hypoalbuminaemia and were prone to suffer from viral infections, such as herpes zoster, or multiple penetrating colonic ulcers in secondary amyloidosis caused by rheumatoid arthritis. Acta Pathol Jpn 1995; 43:59-64.


