PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroentero, 2000; 6(3):461-464
World Journal of Gastroenterology
Copyright©2000 by the WJG Press ISSN 1007-9327

# Renal amyloidosis as a late complication of Crohn's disease: a case report and review of the literature from Japan

Osamu Saitoh[1], Keishi Kojima[1], Tsutomu Teranishi[1], Ken Nakagawa[1], Masanobu Kayazawa[1], Masashi Nanri[1], Yutaro Egashira[2], Ichiro Hirata[1] and Ken-ichi Katsu[1]

**Subject headings** Crohn's disease/complication; renal amyloidosis; amyloid deposits

Saitoh O, Kojima K, Teranishi T, Nakagawa K, Kayazawa M, Nanri M, Egashira Y, Hirata I, Katsu KI. Renal amyloidosis as a late complication of Crohn's disease: a case report and review of the literature from Japan. ***World J Gastroentero***, 2000;6(3):461-464

## INTRODUCTION

Secondary amyloidosis is a rare but serious complication of Crohn's disease (CD ). The incidence of the association of secondary amyloidosis in patients with CD has been reported to be 0.5%-8% in Western countries [1-6]. However, in Japan, the number of patients with CD complicated by amyloidosis is limited. The characteristics of their clinical manifestations and the incidence of association are uncertain. Therefore, we report herein a patient with Crohn's disease who developed amyloidosis 13 years after the onset of CD. The diagnosis of renal amyloidosis was confirmed by renal biopsy. We also reviewed the literature concerning amyloidosis associated with CD in Japan.

## CASE REPORT

The patient was a 29-year-old Japanese female. In May 1985, at the age of 14, she developed diarrhea. In March 1986, she developed fever and arthralgia. A diagnosis of CD was made by endoscopic and radiographic examinations. Thereafter, she received corticosteroids and sulfasalazine. However, hospitaliz ation was required several times. In May 1993, severe stenosis of the as cending colon was found as shown in Figure 1. Therefore, subtotal colectomy, ileocecal resection, and ileosigmoid anastomosis were performed. As shown in Figure 2, surgical specimen of the terminal ileum, cecum, and ascending colon (May 26, 1993) showed thickening of the bowel wall, cobblestone appearance, and longitudinal ulceration. Histological findings showed transmural inflammation and noncaseating epithelioid cell granuloma. In February. 1997, the patient was admitted because of fever, anemia, and hypoproteinemia. As shown in Figure 3, gastrografin enema examination performed on May 8, 1997 showed a stricture aroun d the ileosigmoid anastomosis. The anastomosis and part of the remaining ileum were resected because of the stenosis. Cholecystectomy was also performed becau se of gallstones (the biggest stone measured 11 mm × 5 mm, five stones in total, pigmented). Immediately after surgery, right ureteral stricture due to retroperitoneal involvement was found and indwelling double J-catheter was placed. In August 1998, she was admitted because of anemia and hypoproteinemia. Her family history was unremarkable. Her height was 158 cm and body weig ht was 39.5 kg. Physical examination revealed marked pretibial edema. Laboratory findings included the followings: WBC 7.9 × $10^9$/L, RBC 2.25×$10^{12}$/L, Hb-69 g/L, Ht 0.216, platelet 360 × $10^9$/L, total protein 53 g/L, albumin 11 g/L, CRP 8.9 mg/dL (normal: less than 0.25 mg/dL), serum amyloid A protein (SAA) 235 μg/dL (normal: less than 8 μg/dL), BUN 7.5 mmol/L, creatinine 145 μmol/L, creatinine clearance 0.38 mL/s, and urinary protein 9.3 g/day. Renal biopsy was performed in November 1998. As shown in Figure 4, amyloid deposition was found in the mesangial areas and blood vessels. The deposits were Congo red positive. The positive staining disappeared after pretreatment with potassium permanganate. The deposits immunoreacted with the antibody directed against amyloid A (AA)-amyloid. Colonoscopy revealed small discrete ulcerations around J-pouch. The amyloid deposition was not observed in the digestive tract. The electrocardiogram was normal. Ultrasonography did not show any abnormal findings in the heart. Thyroid was not swollen. Thyroid function tests were normal. Administration of prednisolone (40 mg/day) and 5-aminosalicylate (5-ASA) ( 2.25g/day) normalized serum levels of

[1]Second Department of Internal Medicine, [2]First Department of Pathology, Osaka Medical College, Takatsuki, Japan
Osamu Saitoh MD, Ph.D, graduated from Osaka Medical College in 1979, now an assistant professor of internal medicine specialized in gastrointestinal diseases, having 150 papers published.
This work was supported in part by Grant-in-Aid 10670518 (to Osamu Saitoh) for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan
**Correspondence to:** Osamu Saitoh, Second Department of Internal Medicine, Osaka Medical College, 2-7 Daigakumachi, Takatsuki, Osaka 569-8686, Japan
Tel. 81-726-83-1221, Fax. 81-726-84-6532
Email. saitoh@poh.osaka-med.ac.jp
**Received** 2000-01-17 **Accepted** 2000-02-26

acute phase protein such as CRP and SAA. However, massive proteinuria and hypoalbuminemia persisted. Then, when the dosage of prednisolone was reduced to 10 mg/day, serum CRP and amyloid A protein became positive. Thereafter, azathiopurine (50 mg/d ay) was administered in addition to 5-ASA (2.25 g/day) and prednisolo ne (10 mg/day).

The onset of CD in this patient was May 1985. Diagnosis was made in March 1986. Proteinuria developed in July 1997. Massive proteinuria developed in April 1998. Creatinine clearance was decreased in July 1997. Amyloid deposits were supposed to have already been present in mid 1997.

## DISCUSSION

There is wide geographic variation in the incidence of secondary amyloidosis, occurring in 6%-8% of patients with CD in Northern Europe[2,4,5], 2% in England[3], but only 0.5%-0.9% in the United States[1,6]. However, in Japan, the incidence of secondary amyloidosis in patients with CD remains uncertain. Only 18 Japanese patients with CD complicated by secondary amyloidosis have been reported in the literature from Japan (Table 1)[7-22].

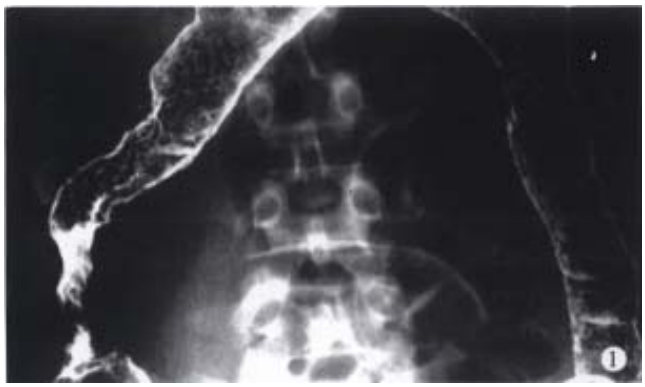
Secondary amyloidosis is caused by extracellular deposition of the N-terminal AA fragment of the circulating acute phase plasma protein SAA. Secondary amyloidosis can complicate any inflammatory condition in which there is a sustained acute-phase response including CD, rheumatoid arthritis, and chronic sepsis. It h as been reported that the activity of the underlying inflammation is an importan t factor in the development and progression of secondary amyloidosis. In the 18 Japanese patients with CD complicated by amyloidosis, there were no patients who maintained prolonged remission. Therefore, in CD as well, the disease activity is considered an important factor in the development of secondary amyloidosis. In the present patient, surgery had already been pe rformed two times as the disease activity could not be controlled by medical tre atment. Nevertheless, serum CRP remained positive. Moreover, in the present patient, the involvement of the retroperitoneum caused right ureteral stricture.

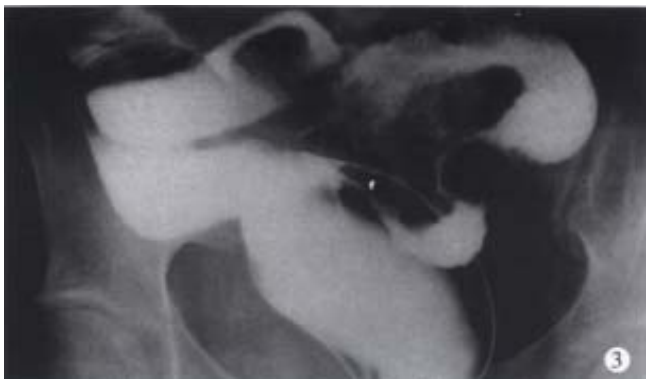
Inflammation is thought to precede the development of secondary amyloidosis. However, the time-course and progression of secondary amyloidosis are not under stood well. In animal experiments, amyloid deposits were found 18h or a few weeks after inflammatory stimuli[23-25]. Various factors have been r eported to influence the susceptibility, onset, and progression of murine amylo idosis[26,27]. It remains controversial whether amyloidosis is a late complication of CD. In the present patient, nephrotic syndrome developed and the diagnosis of secondary amyloidosis was made 13 years after the onset of CD. When proteinuria was initially detected, it had already been 12 years since the onset of CD. In the literature, the time lapse between the onset of CD and the diagnosis of amyloidosis has been reported to range from 3 to 15 years or from 1 to 21 years[28,29]. In 11 of the 18 Japanese patients, more than 5 years had passed after the onset of CD. The longest period was 18 years. Conver sely, in 2 patients, the diagnosis of amyloidosis preceded that of CD. When CD was diagnosed in these 2 patients, the lesion of CD had already become typical. These finding suggest that secondary amyloidosis usually occurs as a late compli cation of CD. However, as the onset of CD is usually gradual, CD and secondary amyloidosis may be diagnosed almost simultaneously.

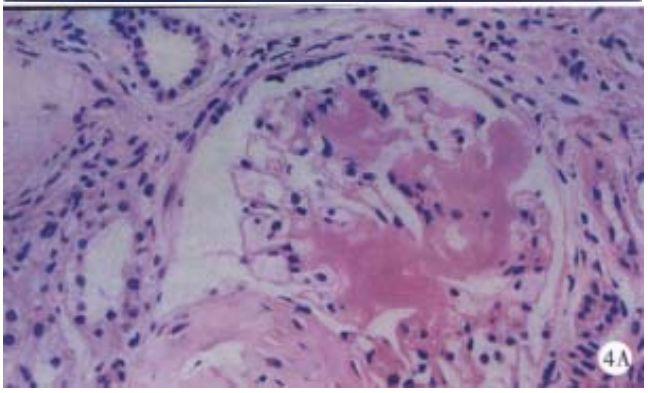
**Table 1 Japanese Crohn's disease patients complicated by second ary amyloidosis**

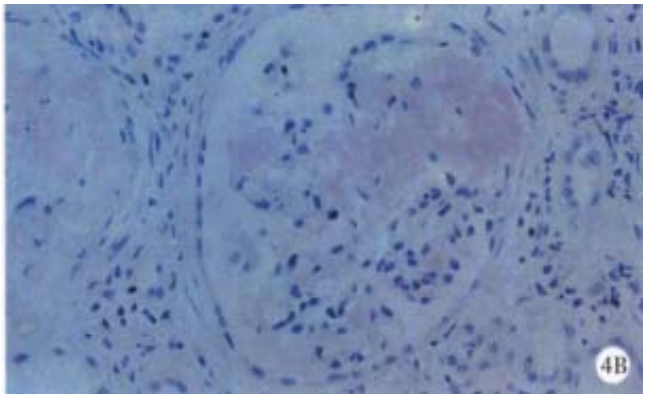
| Case | Age | Sex | Sites of CD | Duration of CD prior to amyloidosis diagnosis | Clinical course of CD before amyloidosis diagnosis | Major clinical manifestation of amyloidosis | type of amyloid | Proteinuria | Author (year) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 23 | M | I,C | 6 year | Not well controlled | Intestinal | AA | Present | Oshima T *et al*. (1988) |
| 2 | 28 | M | I,C | 9 year | Not well controlled | Renal | AA | Present | Tsutsui R *et al*. (1988) |
| 3 | 37 | M | I,C,R | 11 year | Not well controlled | Renal | AA | Present | Araki T *et al*. (1989) |
| 4 | 20 | F | C | 4 year | Not well controlled | Renal | AA | Present | Kikuchi H *et al*. (1989) |
| 5 | 25 | M | I | 0# | | Renal | AA | Present | Momiyama Y *et al*.(1989) |
| 6 | 28 | M | J,C | 0 | | Renal | AA | Present | Takashima H *et al*.(1990) |
| 7 | 24 | M | I | 0 | | Intestinal | AA | None | Itoh T *et al*. (1991) |
| 8 | 44 | M | I | 8 year | Not well controlled | Intestinal | AA | None | Sakai Y *et al*. (1992) |
| 9 | 26 | M | I,C | 13 year | Not well controlled | Renal | AA | Present | Ohwan T *et al*. (1994) |
| 10 | 34 | M | I,C | 15 year | Unknown | Intestinal | AA | None | Yamamoto J *et al*. (1994) |
| 11 | 28 | M | I | 12 year | Not well controlled | Renal | AA | Present | Itoh F *et al*. (1996) |
| 12 | 28 | M | I | 7 year | Not well controlled | Renal | AA | Present | Itoh F *et al*. (1996) |
| 13 | 26 | M | C | 4.5 year | Not well controlled | Renal | AA | Present | Yoshinaga Y *et al*. (1996) |
| 14 | 43 | M | C,R | 15 year | Not well controlled | Renal | AA | Present | Yoshinaga Y *et al*. (1996) |
| 15 | 21 | M | I,C | 3.5 year | Not well controlled | Renal | AA | Present | Horie Y *et al*. (1997) |
| 16 | 43 | M | C,R | 18 year | Not well controlled | Renal | AA | Present | Muro K *et al*. (1998) |
| 17 | 35 | F | C | 0# | | Renal | AA | Present | Taki F *et al*. (1998) |
| 18 | 26 | M | C | 11 year | Unknown | Thyroid | AA | Present | Habu S *et al*. (1999) |
| 19 | 29 | F | I,C,R | 13 year | Not well controlled | Renal | AA | Present | Present case (1999) |

#:The diagnosis of amyloidosis preceded that of Crohn's disease. CD: Crohn's disease, J: jejunum, I: ileum, C:colon, R: rectum, AA: amyloid A





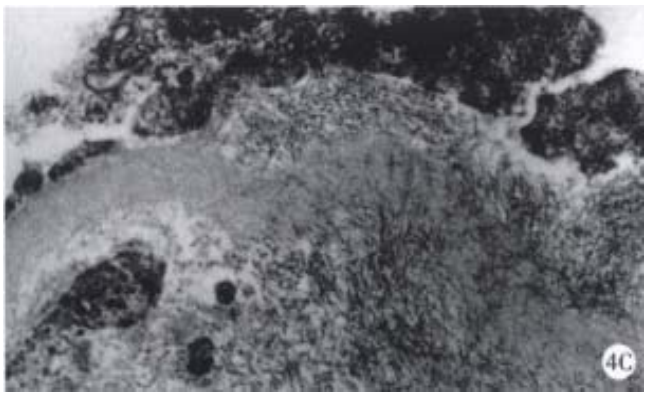




**Figure 1** Barium enema examination perfoemed on March 18, 1993. Stricture associated with cobblestone appearance was seen in the ascending colon. Small inflammatory polyps were observed in the transverse colon and descending colon.

**Figure 2** Surgical specimen of the terminal ileum, ce cum, and ascending colon (May 26, 1993). Thickening of the bowel wall, cobblesto ne appearance, and longitudinal ulceration were found, Histologically, transmur al inflammation and noncaseating epithelioid cell granuloma were found.

**Figure 3** Gastrografin enema examination performed on May 8, 1997. A stricture was seen around the ileosigmoid anastomosis.

**Figure 4** Findings of the renal biopsy.

A. Histological findings (hematocylin and eosin). Amorphous, eosin-stained dep osits were seen in the mesangial areas.

B. Histological findings (Congo red stain). The deposits were Congo red pos itive. Congo red stain showed reddish pink deposits that demonstrated apple-gre en birefringence when examined under polarized light.

C. Electron microscopic findings. Fine fibrils (8 to 10-nm in diameter) arran ged randomly or in bundles were found in the mesangium.

The kidney is involved in the majority of patients with secondary amyloidosis. The resulting renal insufficiency caused a deterioration in the prognosis of the patient. Azathiopurine[30], colchicine[31,32], dimethylsulfoxide[33], and elemental diet[19] have been prop osed as the treatment for secondary amyloidosis. However, the effectiveness of this regimen has not been established. Therefore, prevention or early diagnosis and treatment are important. In 15 of the 18 Japanese patients, the kidney was involved by amyloidosis. And in 13 of the15 patients, renal involvement was the main clinical manifestation of amyloidosis. In only one of the 15 patients[19], the amount of urinary protein decreased to less than 0.3 g/day since the initiation elemental diet therapy. In the remaining 14 patients, however, neither proteinuria nor impaired renal function improved after various therapeutic attempts.

Therefore, regular urine test for proteinuria

would be useful for early diagnosis of amyloidosis regardless of the interval since onset of CD. To prevent the development and progression of secondary amyloidosis, it is probably important to maintain CD in the remission.

**ACKNOWLEDGEMENT** The authors thank the doct ors of Osaka Medical College Hospital for their invaluable contributions to the study of this case.

## REFERENCES

1 Greenstein AJ,Janowitz HD,Sachar DB.The extra-intestinal complication of Crohn's disease and ulcerative colitis: a study of 700 patients. *Medicine Baltimore,* 1976;55:401-412
2 Fausa O, Nygaard K, Elgjo K. Amyloidosis and Crohn's disease. *Scand J Gastroenterol,* 1977;12:657-662
3 Cooke WT, Mallas E, Prior P. Crohn's disease: course, treatment and long term prognosis. *Q J Med,* 1980;49:363-384
4 Lind E, Fausa O, Gjone E, Mogensen SB. Crohn's disease. Treatment and outcome. *Scand J Gastroenterol,* 1985;20:1014-1018
5 Weterman IT, Biemond I, Pena AS. Mortality and causes of death in Crohn's disease. Review of 50 years' experience in Leiden University Hospital. *Gut,* 1990;31:1387-1390
6 Greenstein AJ, Sachar DB, Panday AKN, Dikman SH, Meyers S, Heimann T, Gumaste V, Werther JL, Janowitz HD. Amyloidosis and inflammatory bowel disease. A 50-year experience with 25 patients. *Medicine Baltimore,* 1992;71:261-270
7 Oshima T, Fujimoto K, Kounoue E, Shibuya T, Ishibashi H, Niho Y, Ilda M, Guo K, Nakamura K. A case of Crohn's disease associated with secondary amyloidosis. *J Jpn Soc Internal Med,* 1988; 77:1233-1237
8 Tsutsui R, Okada M, Yao T, Murayama H, Iwashita A, Yokota T. Crohn's disease associated with amyloidosis, report of a case. *Stomach Intestine,* 1988;23:195-201
9 Araki T, Ohmori H, Kosaka K, Ohashi Y. A case of amyloidosis secondary to Crohn's disease. *Jpn J Gastroenterol,* 1989;86:2227-2231
10 Kikuchi H, Saito H, Nakajima H, Uno R, Suzuki K, Sano M, Munakata A, Yoshida Y. A case report of Crohn's disease complicated with renal amyloidosis. *Jpn J Gastroenterol,* 1989;86:2579-2582
11 Momiyama Y, Nagata H, Nakao T. Crohn's disease associated with amyloidosis.A case discovered by persistent proteinuria. *J Jpn Soc Internal Med,* 1989;78:398-403
12 Takashima H, Kisu T, Yamaoka K, Uchida Y, Mori H, Koike Y, Nojiri I, Miyabara S. A case of Crohn's disease associated with nephrotic syndrome due to secondary amyloidosis. *Gastroenterol Endosc,* 1990;32:2393-2398
13 Itoh T, Kawanami C, Kishi K, Kitajima N, Kinoshita Y, Takenaka M, Kodama K, Kishihara M, Inatome T, Inoh T, Tachibana H, Matsumoto Y, Takahashi H, Nakamura T. Crohn's disease associated with secondary amyloidosis: a case report. *Jpn J Gastroenterol,* 1991;88:730-734
14 Sakai Y, Araki Y, Kawakubo K, Kohrogi N, Lida M,Fujishima M. A case of Crohn's disease associated with amyloidosis. *Jpn J Clin Exp Med,* 1992;69:1147-1154
15 Ohwan T, Takano M, Takagi K, Fujiyoshi T, Fujimoto N, Nozaki R, Etoh K, Kikuchi R, Kii F, Tanaka S, Gakiya I, Tsuchihashi N. A case of Crohn's disease in siblings associated with amyloidosis. *J Jpn Soc Coloproctol,* 1994;47:448-454
16 Yamamoto J, Nagae T, Uchida Y, Takenaka K, Sakurai T, Matsui T, Yao T, Yamada Y, Iwashita A. Secondary amyloidosis found by routine duodenoscopy during the course of Crohn's disease, report of a case. *Stomach Intestine,* 1994;29:1437-1443
17 Itoh F, Honda S, Nishimura S, Hinoda H, Imai K. Crohn's disease associated with amyloidosis. Report of two cases. *JJPEN,* 1996; 18:73-74
18 Yoshinaga Y, Nagase S, Kishida M, Odawara M, Tagashira M, Yamawaki Y, Fujino K, matsumoto M, Urakubo N, Morisaki F, Ohta T. Renal amyloidosis secondary to Crohn's disease. Report of two cases. *Med J Onomichi Municipa Hosp,* 1996;12:47-54
19 Horie Y, Chiba M, Miura K, Iizuka M, Masamune O, Komatsuda A, Ebina T. Crohn's disease associated with renal amyloidosis successfully treated with an elemental diet. *J Gastroenterol,* 1997; 32:663-667
20 Muro K, Kobayashi M, Shimizu Y, Kikuchi S, Yamaguchi N, Inadome Y, Watanabe T, Koyama A. A case of systemic AA amyloidosis complicating Crohn's disease. *Jpn J Nephrol,* 1998;40: 284-289
21 Taki F, Tomiyoshi Y, Matsunaga K, Mizuguchi M, Iwakiri R, Ikeda Y, Kou Y, Miyazono M, Sakemi T. A case of Crohn's disease detected by amyloid nephropathy. *Kidney Dialysis,* 1998; 45:135-137
22 Habu S, Watanobe H, Kimura K, Suda T. A case of amyloid goiter secondary to Crohn's Disease. *Endocrine J,* 1999;46:179-182
23 Kisilevsky R, Boudreau L. Kinetics of amyloid deposition. I. The effects of amyloidenhancing factor and splenectomy. *Lab Invest,* 1983;48:53-59
24 Sipe JD, Carreras I, Gonnerman WA, Cathcart ES, de Beer MC, de Beer FC. Chasracterization of the inbred CE/J mouse strain as amyloid resistant. *Am J Pathol,* 1993;143:1480-1485
25 Graether SP, Young ID, Kisilevsky R. Early detection of inflammation-associated amyloid in murine spleen using thioflavin T fluorescence of tissue homogenates: implications for amyloidogenesis. *Amyloid,* 1996;3:20-27
26 Botto M, Hawkins PN, Bickerstaff MC, Herbert J, Bygrave AE, McBride A, Hutchinson WL, Tennent GA, Walport MJ, Pepys MB. Amyloid deposition is delayed in mice with targeted deletion of the serum amyloid P component gene. *Nat Med,* 1997;3:855-859
27 Kindy MS, Rader DJ, Reduction in amyloid A amyloid formation in apolipoprotein-E deficient mice. *Am J Pathol,* 1998;152:1387-1395
28 Lowdell CP, Shousha S, Parkins RA. The incidence of amyloidosis complicating inflammatory bowel disease. A prospective survey of 177 patients. *Dis Colon Rectum,* 1986;29:351-354
29 Rashid H, Blake D, Gokal R, Gooptu D, Kerr DN. The association of renal amyloidosis with regional enteritis (Crohns'disease). Report of two cases and review of the literature. *Clin Nephrol,* 1980; 14:154-157
30 Verbanck J, Lameire N, Praet M, Ringoir S, Elewaut A, Barbier F. Renal amyloidosis as complication of Crohn's disease. *Acta Clin Belg,* 1979;34:6-13
31 Ravid M, Shapira J, Kedar I, Feigl D. Regression of amyloidosis secondary to granulomatous ileitis following surgical resection and colchicine administration. *Acta Hepatogastroenterol,* 1979; 26:513-515
32 Meyers S. Systemic amyloidosis complicating inflammatory bowel disease. *Gastroenterology,* 1997;113:731
33 Ravid M, Shapira J, Lang R, Kedar I. Prolonged dimethylsulphoxide treatment in 13 patients with systemic amyloidosis. *Ann Rheum Dis,* 1982;41:587-592

Edited by You DY