Virchows Arch [Pathol Anat] (1986) 409:3–9

Virchows Archiv A

Glomerular lesions associated with the Crow-Fukase syndrome

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Summary. Three cases of the Crow-Fukase syndrome without radiographic changes of multiple myeloma are reported, with special reference to the glomerular changes seen. Proteinuria was detected in one case, although decreased renal function was observed in all (GFR: 41.0, 62.0, 74.1 ml/min respectively) at the time of renal biopsy. Glomerular changes were similar in all three cases. The main characteristic changes were mesangial proliferation and thickening of the glomerular capillary walls. Pictures by light microscopy were therefore similar to that of MPGN. On electron microscopy, the thickened capillary walls showed circumferential mesangial interposition and the subendothelial zone was electron-lucent and contained small dense granules or flocculent deposits. By immunofluorescent microscopy, no immunoglobulins, complement components or light chain were detected in the glomeruli except in one case.

Key words: Crow-Fukase syndrome – MPGN like lesion – Subendothelial deposits

Introduction

Since Fukase et al. reported a patient who had polyneuropathy, edema, hypertrichosis, skin pigmentation and solitary plasmacytoma in 1968 (Shimpo et al. 1968) over hundred cases with similar symptoms have been reported, mainly in Japan (Imawari et al. 1974, Iwashita et al. 1977; Nakanishi et al. 1984). Outside Japan, the number of case reports dealing with a similar syndrome (Crow 1956; Trentham et al. 1976; Meshkinpour et al. 1977; Driedger and Pruzanski 1980; Bardwick et al. 1980) has been increasing lately. Nakanishi et al. reviewed 102 cases of this syndrome and proposed to call the group the Crow-Fukase syndrome (Nakanishi et al. 1984). Al-

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though about 50% of the patients with this syndrome showed proteinuria, reports of renal histopathology were scanty and morphological pictures reported were vague.

We experienced three cases which were diagnosed as exhibiting this syndrome. All three cases had renal disease and their renal biopsies showed by light and electron microscopy, glomerular lesions similar to membranoproliferative glomerulonephritis (MPGN).

The following is a description of three cases with special reference to the characteristic glomerular lesions.

Case reports

All three cases were diagnosed as exhibiting the Crow-Fukase syndrome according to the clinical manifestations listed in Table 1.

Case 1. A 45 year-old farmer (male) had noticed facial and pretibial edema and sensory disturbance in the soles of the feet since August 1975, before proteinuria was detected in September 1977. In May of 1978, the patient was admitted to the Hospital of the University of Tsukuba with pleural effusion and ascites as well as the previous symptoms. After admission, he was diagnosed to have the Crow-Fukase syndrome because of clinical manifestations shown in Table 1. B.P. was 128/82 mm Hg. Laboratory findings showed neither M-protein nor Bence Jones protein. Whole body bone survey revealed no evidence of multiple myeloma. A biopsy

Table 1. Clinical manifestations

	Case 1	Case 2	Case 3
Polyneuropathy			
Peripheral Neuropathy	+	+	+
Papilledema	+	−	+
Increased CSF Protein (mg/dl)	172	150	182
Anasarca			
Peripheral Edema	+	−	+
Ascites	+	−	+
Pleural Effusions	+	−	+
Skin Changes			
Hyperpigmentation	+	+	+
Hypertrichosis	−	−	+
Thickening	+	+	+
Endocrinopathy			
Gynecomastia	−	+	+
Glucose Intolerance	−	+	−
Dysglobulinemia			
M-Protein	−	−	+
Bone Lesions	−	−	−
Organomegaly			
Hepatomegaly	+	+	+
Lymphadenopathy	+	+	+
Others			
Finger Clubbing	+	+	+

of the cervical lymph node showed proliferation of histiocytes and the increase of capillaries. An accumulation of small round cells (mainly plasma cells) was also seen in the sinuses of the lymph node. Cerebrospinal fluid (CSF) protein was 172 mg/dl; 50 g glucose tolerance test (50 g GTT) and serum complement were within normal limits. Urine protein was 0.3–0.5 g/day and renal function was decreased to PSP 5% (15 min) and GFR 41.0 ml/min. BUN: 39.2 mg/dl, S-Cr: 1.7 mg/dl. A renal biopsy was performed and glomerular lesions are described later.

The pleural effusion, ascites and edema gradually decreased and desappeared after the administration of furosemide. Also, BUN and S-Cr gradually decreased to 23.0 mg/dl and 1.5 mg/dl, respectively. After the administration of prednisolone (initial dose 40 mg/day), a neurological improvement was noticed in the proximal parts of the extremities. Renal functions improved as follows: GFR 81.0 ml/min, RPF 315.9 ml/min, and FF 0.26 as of December 12. After discharge on December 12, 1978, the patient was treated with 6 mg/day of paramethone until February, 1981. Renal function has considerably improved as the following figures show; PSP 32% (15 min), GFR 97.1 ml/min, RPF 363.3 ml/min on Feb, 1980. BUN 20.4 mg/dl, S-Cr 0.6 mg/dl. In 1985, urine protein was under 20 mg/dl and occult blood was negative.

Case 2. A 62 year-old farmer (male) had noticed sensory distrubance and muscular weakness in both legs, with gradual progression since 1975, when he was finally unable to walk, and he was admitted to hospital in 1978. Muscular atrophy and weakness were marked especially in peripheral parts. Blood pressure was 166/100 mm Hg. Clinical findings are listed in Table 1. CSF protein was 150 mg/dl. There was no sign of myeloma in a general bone x-ray survey. The number of plasma cells in the bone marrow was 2.0%. Histopathology of an inguinal lymph node showed angiofollicular hyperplasia. Serum complement was within normal limit. Urinalysis revealed no proteinuria nor glucosuria. Renal function was decreased to PSP 13% (15 min), and to GFR 62.0 ml/min. Renal lesions are described later. Neither M-protein nor Bence Jones protein were detected. 50 g GTT showed diabetic pattern (before: 133 mg/dl, 60 min: 203 mg/dl, 120 min: 269 mg/dl).

After the administration of prednisolone (initial dose: 40 mg/day), the sensory disturbance and muscular weakness showed considerable improvement and urinalysis continued to show no proteinuria. A maintenance dose of prednisolone (5 mg/day) was administered at an outpatient clinic until April, 1983. On August 1980, PSP was 27% (15 min). In 1985, urinalysis showed no proteinuria and urinary sugar: (+ +). BUN 14.7 mg/dl, Cr 0.7 mg/dl. He had slight sensory disturbance on legs and had diet therapy for diabetes mellitus.

Case 3. A 53 year-old farmer (male) noticed impaired sensation on both soles of the feet from 1980 and developed edema in the lower extremities. Thereafter a disturbance in his gait appeared and gradually increased. He was admitted to hospital in November, unable to walk. B.P.: 140/90 mm Hg. Serum analysis revealed the elevated IgG (1,717 mg/dl) and M-protein of IgG (λ) was noticed by immunoelectrophoresis. Bence Jones protein was detected. A general bone survey revealed no findings of multiple myeloma. Pathological study of an axillary lymph node showed Castleman-like lymphadenitis. Urinalysis showed no albuminuria. Urine sediment RBC: 1–5/hpf, WBC: 1–5/hpf, Casts: (−), BUN 14.2 mg/dl, S-Cr 0.8 mg/dl, GFR: 74.1 ml/min, RPF 320.3 ml/min. Renal pathology is described later. After admission, the pleural effusion and ascites increased, leading to general deterioration. 60 mg/day of prednisolone was administered beginning on January 19, 1981. However, the general condition of the patient deteriorated and he died of a complication of DIC on February 18, 1981.

Renal pathological findings. Glomerular lesions are essentially the same in the three cases. The most characteristic changes are mesangial enlargement with mesangial cell proliferation and thickening of glomerular capillary walls (Fig. 1A, B). The mesangial proliferation is most intense in case 1 and a tendency to make lobulation is noticed (Fig. 1A). Congo red staining reveals no amyloid deposition in all three cases.

On electron-microscopy the subendothelial zone is electronlucent and contains small dense granules or flocculent deposits. These flocculent (Fig. 3B) or fine granular (Fig. 3C) material has no periodicity. The thickened capillary walls show circumferential mesangial interposition (Figs. 2, 3). Dense deposits are also seen in the mesangial area and foot processes disappear.

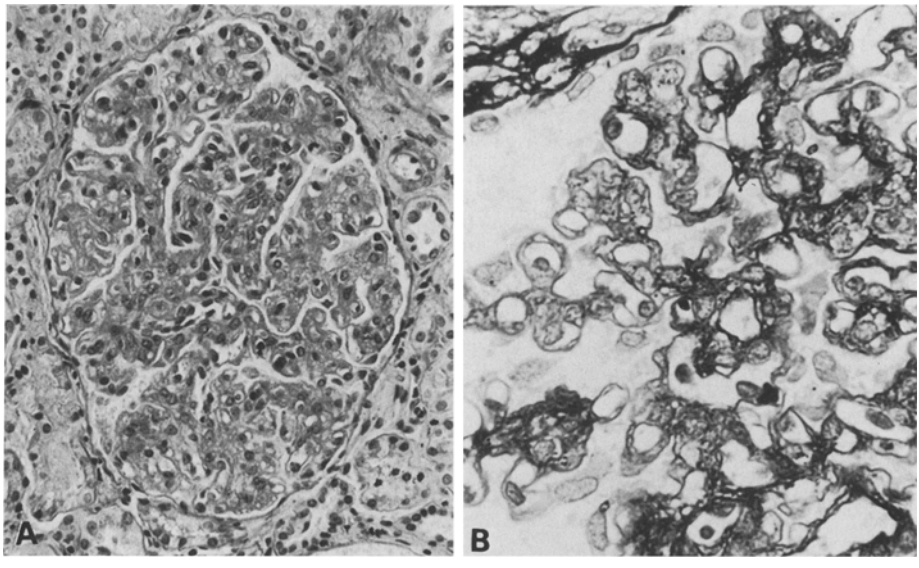

Fig. 1. Photo **A** shows the swelling and lobulation of glomerulus due to increase of mesangial cells and matrix. A thickening of glomerular capillary walls is also seen. (PAS × 200 Case 1) Photo **B** shows the thickening and double contours of glomerular capillary walls. (PAM × 400 Case 2)

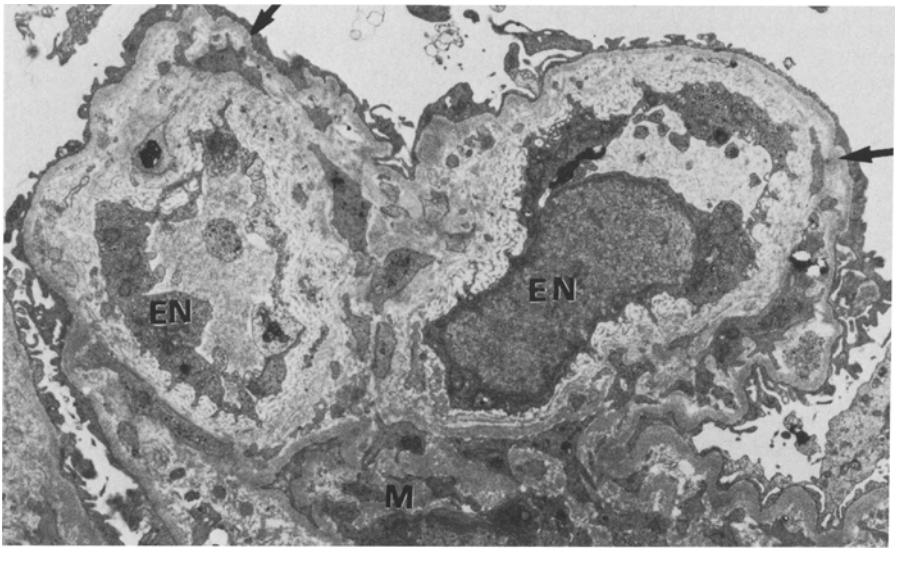

Fig. 2. The findings of electron microscopy in case 1. The thickened capillary walls consist of circumferential mesangial interpositions (*arrows*) and have abundant subendothelial deposits. *En*: endothelial cell, *M*: mesangium (× 5,000 Case 1)

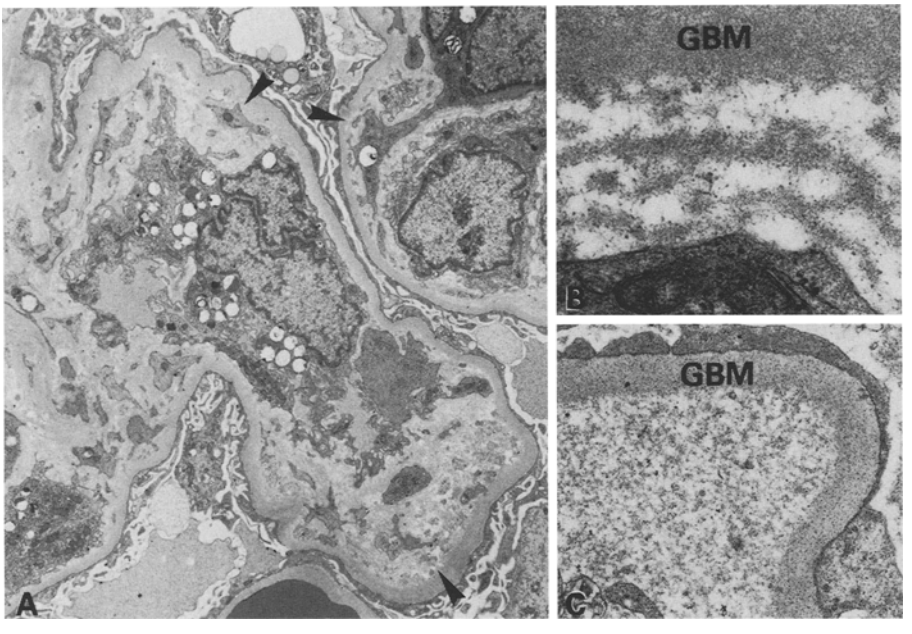

Fig. 3. Photo A shows abundant subendothelial deposits and mesangial interposition is also seen (arrowheads). (× 5,800 Case 3) Subendothelial deposits are flocculent (Photo B) or fine granular (Photo C). Photo B: case 1 (× 26,000). Photo C: case 3 (× 10,000) GBM: Glomerular basement membrane

The total numbers of glomeruli are 83, 50, 60 in cases 1, 2, 3 respectively. Small numbers of scattered obsolescent glomeruli are also seen.

The interstitium contains focal and slight fibrosis and a small number of chronic inflammatory cells.

However, there was a discrepancy in the findings by immunohistopathology. Case 1 and Case 2 revealed no fluorescence for IgG, IgA, IgM, IgE, light chain (κ, λ), C1q, C4. C3, fibrinogen in the capillary walls or mesangium, even after re-examination. Case 3 revealed slight localization of IgA, IgM, C3 along the capillary walls; for fibrinogen and light chain (λ), the staining was segmental, less intense, and negative for IgG, C1q, C4, light chain (κ).

Discussion

In Japan, much attention has recently been given to the Crow-Fukase syndrome (Nakanishi et al. 1984), a unique, multisystemic syndrome characterized by polyneuropathy, anasarca, skin changes, endocrinopathy, dysglobulinemia, and organomegaly. Over 100 cases have been reported in Japan since the first Japanese case was presented in 1968. Outside Japan, many similar cases (Trentham et al. 1976; Meshkinpour et al.; Driedger et al. 1980; Bardwick et al. 1980) have also been reported since the first case was reported by Crow (1956).

The Crow-Fukase syndrome is divided into two groups, one with radiographic changes of myeloma and the other without them. The latter group is classified into two subgroups, one with M-protein and the other without

(Nakanishi et al. 1984). The three cases that we experienced can be regarded as cases without radiographic changes of myeloma. One of these three cases (Case 3) had Bence Jones protein as well as M-protein of IgG (λ).

The renal disorder of this syndrome has not been emphasized, and only a few case reports have described the pathological changes of the renal disease. However, a careful review of these case reports of this syndrome revealed that there were more cases with renal disorder than initially expected. In reviewing the literature describing the Crow-Fukase syndrome (Nakanishi et al. 1984; Shibata and Okada 1985), thirty cases with the description of urinalysis were found. In fifteen of these cases proteinuria was found. In all 15 reported cases in which BUN was described, 5 cases showed over 20 mg/dl of BUN. In all 22 reported cases with the description of PSP, eleven cases showed under 25% (15 min) of PSP. These findings have suggested that some patients may have had renal disturbances, although they may not have been serious.

A few reports on glomerular histopathology are found in Japan but consistency is not being established in their observations. The reported glomerular changes are the thickening of arteriole and glomerular capillary wall with scattered hyalinized glomeruli (like diabetic glomerulosclerosis) (Iwashita et al. 1977), glomerulonephritis of membranous type (Shimizu et al. 1977), the thickening of GBM, marked swelling of endothelial cells and narrowing of glomerular capillary lumen (Horigami et al. 1977), idiopathic mesangioproliferative lobular glomerulonephritis (Yuasa et al. 1977) and nephropathy similar MPGN (Harada et al. 1981). The main glomerular lesions obtained through light microscopy are the thickening of glomerular capillary walls and the increase of mesangial cells and such glomular lesions were also seen in our cases.

In these three cases, double contours were obviously observed along the thickened glomerular capillary walls and circumferential mesangial interposition was also observed by electron microscopy. These morphological characteristics are similar to MPGN. But except for case 3, which revealed M-protein (IgG), no depositions of immunoglobulins or complements were observed in the glomeruli of the Crow-Fukase syndrome. These findings are different from idiopathic MPGN.

By electron microscopy, the electron lucent area could be observed in subendothelial space and there, electron dense material was seen in granular or flocculent pattern. The electron dense material did not show the periodicity which is seen in fibrin or collagen fiber.

The light chain nephropathy is known as one of the diseases which show glomerular lesions similar to MPGN (Scully et al. 1981; Heptinstall 1983). Although there are some similarities of the glomerular lesions in these three cases and that of light chain nephropathy, there is no deposition of light chain by fluorescent microscopy except for slight segmental deposition of light chain (λ) in case 3.

The Crow-Fukase syndrome has plasma cell dyscrasia and it is suggested that the plasma cells may secrete an unknown substance that is toxic to many organs such as the peripheral nervous system, endocrine glands, the

skeleton, and reticuloendothelial and immunohematopoietic systems (Nakanishi et al. 1984). A nephropathy which has characteristic subendothelial deposits may be one of the multiorgan disorders of this syndrome.

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Accepted January 13, 1986