Guillain-Barré Like Syndrome Associated with Acute Renal Failure and Thrombocytopenia Following Acute Viral Hepatitis A

We reported a 43-year-old woman who showed a Guillain-Barré like syndrome associated with acute renal failure (ARF) and thrombocytopenia following acute viral hepatitis A (HA). The clinical feature was acute progressive and of ascending symmetric paraparesis which developed 5 days after gastrointestinal infection. Neurologic examination showed flaccid paraparesis, areflexia in all extremities and limitation on the straight leg raising test. Laboratory examinations showed the evidences of ARF, thrombocytopenia and HA. EMG findings suggested a polyradiculopathy. Renal biopsy showed the findings of acute interstitial nephritis, acute tubular necrosis and IgA deposition nephropathy. She was treated by plasmapheresis and platelet transfusion, then showed a rapid improvement, and has been well without further complication after discharge.
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Key Words : *Guillain-Barré like syndrome, Acute renal failure, Thrombocytopenia, Acute viral hepatitis A*

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INTRODUCTION

Guillain, Barré, and Stohl, in 1916, gave the syndrome its eponym (the Guillain-Barré syndrome, GBS), and since then some limited understanding of the pathophysiology of postinfective polyradiculoneuritis has evolved. Approximately 60% of the cases of GBS are triggered by viral syndrome that mostly affect the respiratory tract (either upper or lower) and, less often, the gastrointestinal tract. GBS is a disorder found frequently in the neurological field, however the syndrome associated with acute renal failure (ARF) and thrombocytopenia following acute viral hepatitis A (HA) is rarely found. We present a case and review of the literature on reported cases.

CASE REPORT

A 43-year-old woman was admitted to the department of neurology via the emergency room due to acute onset progressive ascending paraparesis 5 days after gastrointestinal infection. She was a housewife and had no significant past or social history.

On general examination, her vital signs were intact and other physical examinations showed no abnormal findings. Respiratory difficulty was absent. Motor examination showed a flaccid paraparesis (3/5) but muscle atrophy was absent. She showed a limitation on the straight leg raising test (SLRT) (45°/45°). She showed areflexia in all extremities, but sensory and cerebellar dysfunction were absent.

Initial cerebrospinal fluid (CSF) analysis done 1 day and 10 days after admission did not show any abnormal findings. Initial electrodiagnostic tests done 1 day after admission showed an absence of H-reflex bilaterally, and follow-up studies done 17 days after admission showed an absence of bilateral median F-wave additionally, but the latencies of bilateral tibial F-wave were within normal limits (right 44.4 msec, left 43.4 msec). And denervation potential was absent in the muscles of paraspinal region and all the extremities. The results of motor and sensory nerve conduction studies were normal, and conduction block was absent. Blood chemistry showed elevated AST (1500 U/L), ALT (1748 U/L), & bilirubin (total : 2.7 mg/dl, D-bilirubin 1.2 mg/dl) levels. Serum and CSF hepatitis A IgM antibody (Ab) were positive, but hepatitis B and C markers were negative. Initial urinalysis showed microscopic hematuria, but became normalized several days after admission. However BUN/creatinine level had elevated progressively for several days after admission up to 85/10 mg/dl. Hemoglobin content was 8.2 g/dl and platelet count was $33 \times 10^3/\mu l$. Peripheral blood smear showed normocytic normochromic anemia,

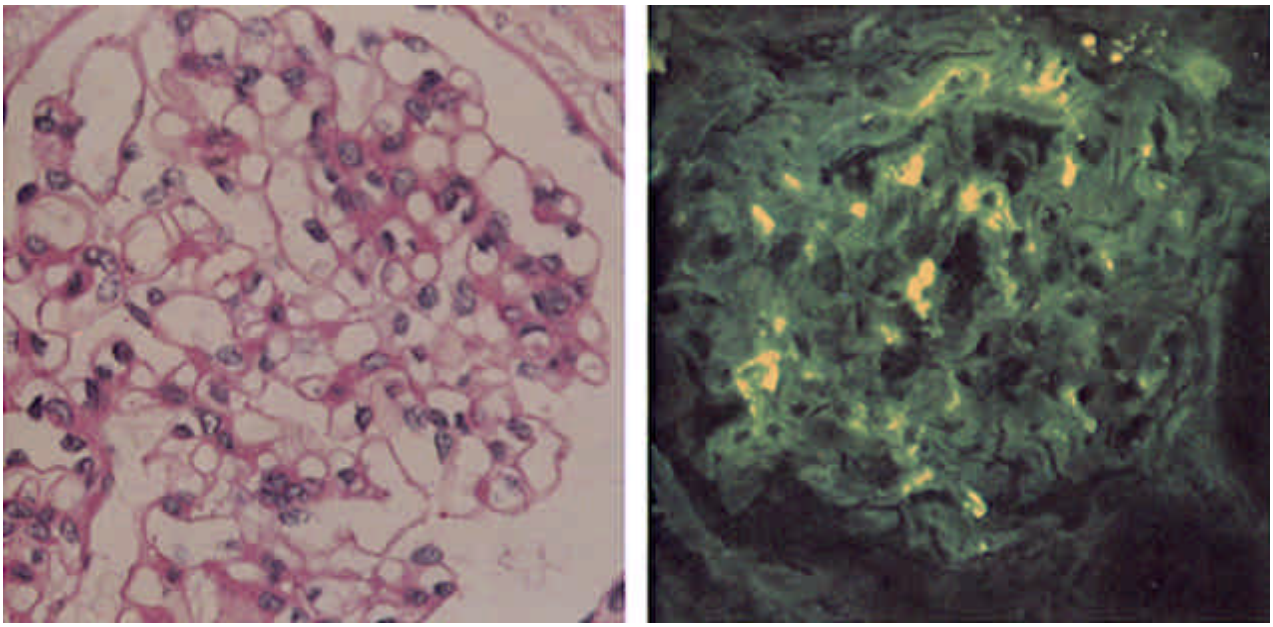

Fig. 1. Glomerulus reveals mild mesangial widening with cellular proliferation (left). Granular fluorescent IgA deposits are in the mesangium (right).

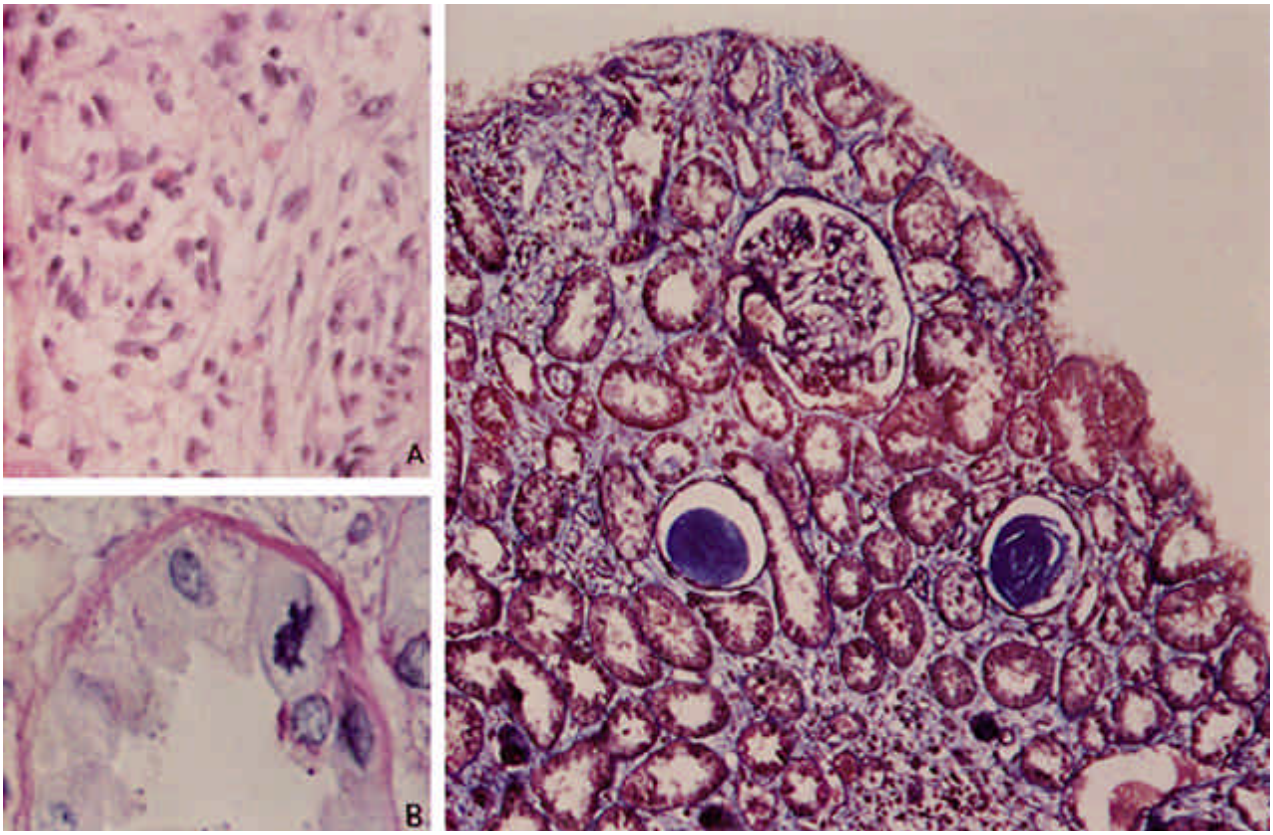

Fig. 2. Interstitium is edematous and infiltrated by mononuclear cells and few eosinophils. Epithelial cells are attenuated in some tubules and few mitotic figures are noted (inset).

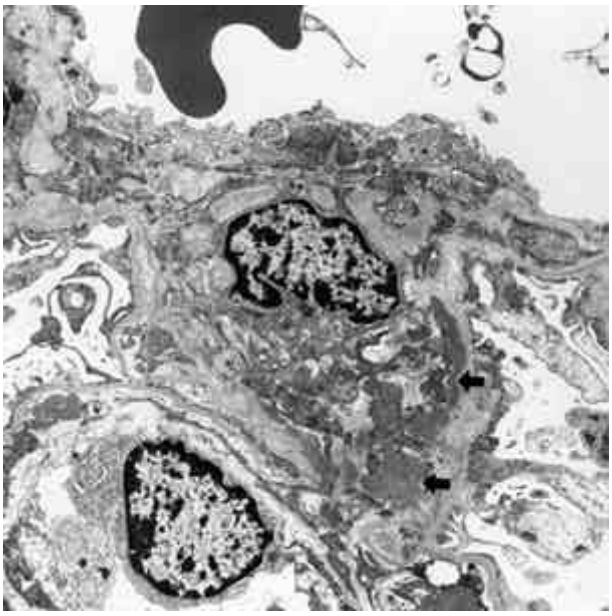

Fig. 3. Electronmicroscopically, dense deposits are in the mesangial area (arrow) (original magnification, ×5,000)

toxic change of granulocyte and thrombocytopenia.

Renal biopsy was done 9 days after admission. Ten glomeruli were examined. All glomeruli had similar changes. Mild mesangial cell proliferation and widening of the mesangial area were seen. A few, tiny fuchsinophilic deposits on trichrome stain were discernible. Mononuclear cells and a few eosinophils had infiltrated along the interstitium. Tubular epithelial cells were mostly attenuated, and were detached in some area. Few mitoses were noted (Fig. 1, 2, 3).

Plasmapheresis was started after 2 days and subsequently on days 3, 5, and 8 after admission. Platelet pheresis were also performed twice. Motor power and SLRT began to improve 3 days after initial treatment, and all other laboratory findings became normalized subsequently. Nine days after admission, motor power of the lower extremities became 4.5/5 bilaterally and SLRT became 90°/85° in right and left, respectively.

Nineteen days after admission she was discharged, and she has enjoyed a normal life. Follow-up examination done 70 days after the onset of the disease showed continued areflexia in all extremities but normal responses in electrodiagnostic test including H-reflex and F-wave.

DISCUSSION

This acute inflammatory polyneuropathy-GBS-occurs in all parts of the world and during all seasons. It affects children and adults of all ages and both sexes. Its cause is still unknown. A mild respiratory or gastrointestinal infection precedes the neuritic symptoms by 1 to 3 weeks (sometimes longer) in about 60% of the patients (1).

The diagnostic criteria for GBS is as followings: Features required for diagnosis are progressive weakness for both legs and arms and areflexia. And clinical features supportive of diagnosis are progression over days to 4 weeks, relative symmetry of signs, mild sensory symptoms or signs, cranial nerve involvement(bifacial palsies), recovery beginning 2~4 weeks after progression ceases, autonomic dysfunction and absence of fever at onset. And laboratory features supportive of diagnosis are elevated CSF protein with < 10 cells/μl and electrodiagnostic features of nerve conduction slowing or block (2).

The symptoms and signs of our case were clinically similar to those of classic GBS, i. e. onset of disease after gastrointestinal infection, absence of fever at onset, acute progressive and of ascending paraparesis, areflexia, limitation of SLRT, progression over days, symmetry of signs, recovery beginning about 2 weeks after onset, absence of bilateral H-reflex and median F-wave, and rapid improvement after plasmapheresis.

In classic GBS, the CSF protein content is elevated in most patients with GBS but may be normal in the first few days after onset (3). Initial and follow-up CSF protein content were not elevated in our case. It might be due to the fact that initial CSF study was performed early in the course of disease and the effect of early performed plasmapheresis. And the absence of any cranial nerve dysfunction and denervation potentials in all tested muscles, which were not clinically consistent with the classic GBS, might be also due to the arrest of progression of GBS by early performed plasmapheresis and mildness of disease severity. Sural nerve biopsy was not performed. Therefore our case was Guillain-Barré like syndrome (GBLS).

Although viral hepatitis is common in Korea, hepatitis-related GBS is not commonly seen, and there is little literature on the association between hepatitis and GBS.

An acute polyneuritis, indistinguishable clinically and pathologically from the GBS type, may be associated with an obscure viral hepatitis. The polyneuritis usually follows jaundice by several days or weeks and probably has the same relation to it or to preceding respiratory or intestinal infections. The type of hepatitis often remain unclear. There are usually no antibodies to the common types of viral hepatitis (4).

Sporadic case reports linking GBS and acute infective hepatitis date back to 1929 when Lemierre and Lhemitte drew attention to a young male patient who appeared to have an acute infective hepatitis complicated by a rapidly progressive cranial polyneuritis and flaccid

paralysis of the lower limb. Lelong and Bernard (5) reported another case of ascending polyneuritis in a patient during a local epidemic of infectious hepatitis, and Newman (6) noted that mild polyneuritic signs may precede the onset of epidemic jaundice. In his review of 1100 cases of GBS, Leneman listed over 36 infective agents possibly associated with the prodromal illness in cases of GBS. From Leneman's large review (7), 11 cases were associated with viral hepatitis of unknown type. An additional 26 cases of viral hepatitis-associated GBS were found in the literature between 1944 and 1980 and reviewed by Berger et al. (8). Only 4 cases of GBS associated with acute viral hepatitis reported after 1965 have been linked with hepatitis B.

It was not until 1981 that a case of GBS was associated with HA infection. The presence of HA IgM Ab points to recent infection with HA virus, to which both the acute hepatitis and acute polyradiculoneuropathy could be attributed (9). Our patient showed the presence of HA IgM Ab in serum and CSF.

Bosch et al. (10) reported 2 patients among 167 GBS had high titers of HA virus specific IgM Ab in serum. The patients had jaundice and laboratory evidence of liver involvement before the onset of the neurologic disease. Igarashi et al. (11) reported a case of GBS associated with acute HA, who showed a HA IgM Ab in CSF. And they suggested that the GBS might be related to the immunopathogenetic mechanism of HA virus infection. Tabor (12) reported seven cases of serologically documented HA has been associated with GBS, who all recovered with mild neurologic residua in four. Endoh et al. (13) reported a case of GBS following acute HA, who showed HA-IgM Ab and HA Ab in CSF and then the titers decreasing with neurologic improvement. And they suggested that GBS might possibly be related to HAV infection. Ono et al. (14) suggested that clinical features of GBS follow HA could be summarized as followings : 1) most of the patients are men, 2) GBS develops within 14 days after the onset of HA, 3) facial nerve palsy is frequently present, 4) proprioception is likely impaired in addition to superficial sensation, 5) the outcome of neuropathic symptoms are uniformly good, regardless of the degree of liver dysfunction as evaluated on the basis of alanine aminotransferase levels. And they also suggested GBS following HA essentially does not differ from typical GBS. But Xie et al. (15) reported that there was lack of association between HA and GBS during a major epidemic of HA infection.

Our case presented general fatigue for several days before admission and laboratory findings showed elevation of AST, ALT and bilirubin level and presence of IgM Ab to HA in serum and CSF. Therefore our case suggested that HA infection was preceded and subsequently GBS had begun as above mentioned reports except Xie et al. (15).

In 1918, 2 years after the original description of the GBS, Bradford et al. (16) noted the existence of nephritis in each of 6 autopsied cases of acute infectious nephritis. Reports of renal involvement in GBS in the literature, however, have been rare. Uremia was found in only 7 patients in Leneman's review of 1100 cases and albuminuria was involved in 6% of 50 fatal cases (17). Renal involvement of any type in GBS is not commonly seen clinically, but it may be manifestated in different ways. While early autopsy studies have documented the presence of nephritis in patients dying from acute infectious polyneuritis, other clinicopathologic studies have provided conflicting results. Subtle clinical findings such as intermittent hypertension and microscopic hematuria have been found and histologic evidence of acute glomerulonephritis suggests that renal involvement may be more common than previously thought (18).

This GBLS associated with acute interstitial nephritis, acute tubular necrosis, and IgA deposition nephropathy may be the first case in our knowledge. Likewise, GBS combined with thrombocytopenia has not been commonly reported.

There have been a few reports about acute HA associated with ARF (19, 20). They suggested that the mechanisms responsible for renal failure in liver diseases could be multifactorial ; immune complex-mediated nephritis and/or endotoxemia have been considered. Watanabe et al. (21) reported that a case of ARF associated with type A acute hepatitis responded dramatically to plasmapheresis. Chio and Bakir (22) reported an ARF in HA, and they suggested that renal failure resulted from viral-induced injury, either directly or mediated by immune complexes. Konishi et al. (23) reported that the patients with acute HA have had symptoms of appetite loss, nausea, vomiting and/or diarrhea, causing hypovolemia, and hepatic dysfunction caused discontrol of vasoactive hormones and lead to disturbance of renal circulation. Subsequently, acute tubular necrosis and ARF could occur. Takeshita et al. (24) reported a case of sporadic acute HA associated with ARF, due to mesangioproliferative glomerulonephritis and interstitial nephritis and reported fine granular deposits of IgA on immunofluorescent studies like our case. One major etiology for the mesangial IgA deposition was liver dysfunction, which elevated serum IgA by disturbing hepatic IgA degradation function.

Kleinman and Friedman (25) reported a transient autoimmune thrombocytopenia associated with acute infectious HA, and Narumi et al. (26) reported an acute hepatitis presenting severe thrombocytopenia. Piccinini et al. (27) reported hematologic complications including

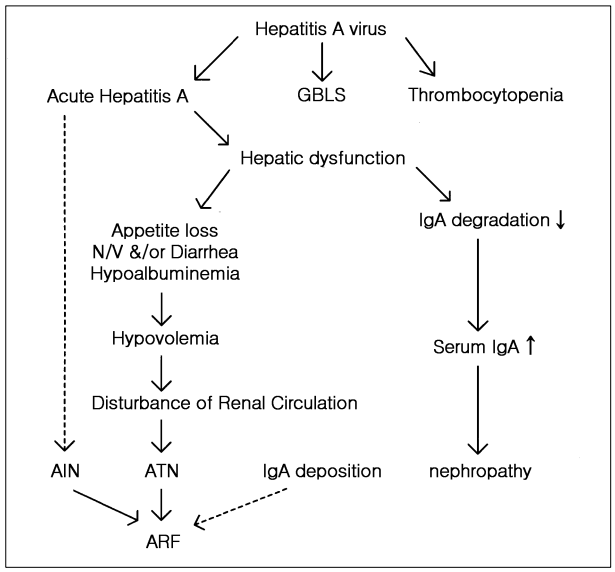

Fig. 4. Pathogenesis of GBLS associated with ARF and thrombocytopenia following acute viral hepatitis A. A solid line means a direct effect. A dotted line means an indirect effect. AIN : acute interstitial nephritis, ATN : acute tubular necrosis, ARF : acute renal failure, N/V : nausea/vomiting.

thrombocytopenia of viral hepatitis. Imatake et al. (28) reported a case of HA associated with thrombocytopenia, leukopenia, and ARF.

It should be noted that our patient presented a GBLS associated with ARF and thrombocytopenia following acute HA, for which we give the suggested mechanism in Fig. 4. HA virus caused acute HA, GBLS and thrombocytopenia, and subsequently hepatic dysfunction caused an ARF. A dotted line means an indirect effect and a straight one means a direct effect.

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