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Two Cases of Systemic Capillary Leak Syndrome that were Treated with Pentastarch

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Systemic capillary leak syndrome (SCLS) is a condition that's caused by the shift of fluid and protein from the intravascular space to the interstitial space as a result of repetitive episodes of capillary hyperpermeability. The pathogenesis of SCLS is still unclear, but there's recently been a report showing this syndrome in association with monoclonal gammopathy. This syndrome can be a fatal disease because cardiovascular collapse can occur in the initial capillary leak phase. Although theophylline, diuretics, terbutaline, steroids, calcium antagonist, Ginkgo biloba extracts and plasmapheresis have been suggested as medication, none of them have been proven to be effective. Considering that this disease is self-limiting, conservative treatment in the acute phase is believed to be very important. Because hypoalbuminemia is very a common manifestation of SCLS, Pentastarch, which has a higher molecular weight than albumin, could be efficient to prevent cardiovascular collapse. We used 10% Pentastarch during the acute SCLS attacks of 2 patients and the patients both showed a dramatic response. Pentastarch may be helpful to treat SCLS in its initial capillary leak phase by the elevating blood pressure, and this might contribute to somewhat decreasing the acute mortality of SCLS.

Key Words : Systemic capillary leak syndrome, Pentastarch, Cardiovascular collapse

INTRODUCTION

Systemic capillary leak syndrome (SCLS) is a disorder characterized by unexplained episodic capillary hyperpermeability, which causes the shift of fluid and protein from the intravascular space to the interstitial space[1]. It is a rare, but often fatal disease[1]. Since no effective treatment has so far been found, this disease could lead to death if the blood pressure is not increased during the initial capillary leak phase. We experienced two cases where treatment with using 10% pentastarch elevated the blood pressure and eventually improved the patients, who were both in the acute phase of SCLS.

CASE REPORT

Case 1

A 37 year-old woman came to our hospital presenting with episodes of resting dyspnea, oliguria and anasarca, which had started one day previously. She had developed upper respiratory tract infection 3 days before admission, but she didn't get any medication. She was alert with a systolic blood pressure of 40 mmHg, heart rate: 110 beats/min, respiratory rate: 35 breaths/min and body temperature: 37℃. Auscultation proved her breath sounds were normal. The laboratory finding showed hemoglobin: 19.2 g/dL, hematocrit: 53%, leukocytes: 17,400/mm^2, platelets: 147,000/mm^2, blood urea nitrogen/

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creatinine (BUN/Cr): 32.8/1.9 mg/dL, total protein/albumin: 3.7/1.7 g/dL, C-reactive protein (CRP): 3.1 mg/L and the monoclonal IgG-kappa was positive. The laboratory test performed later showed C3/C4: 34.0/6.9 mg/dL and IgA/G/M: 101/810/102 IU/mL, respectively. The C1 esterase inhibitor level was normal and bone marrow biopsy showed no evidence of multiple myeloma. Despite intravenous injection of a combination of 9 L of normal saline solution and inotropic drugs, her systolic blood pressure did not increase and she developed respiratory failure resulting from pulmonary edema. The central venous pressure (CVP) was 3 cmH_2O. We stopped using normal saline solution and started using 10% pentastarch (Pentaspan inj, Jeilpharm, Korea). After we started infusing 10% pentastarch 500 mL every 8 hours, her blood pressure began to increase. We also used intravenous methylprednisolone, aminophylline and calcium. Her blood pressure and the CVP recovered to the normal levels the next day. The hemoglobin level measured at that time was 16.8 g/dL, with a hematocrit of 47%, leukocytes: 26,200/mm^2, platelets: 93,000/mm^2, BUN/Cr: 35.4/1.2 mg/dL and prothrombin time (PT): 2.8 INR. We thought that PT prolongation was a side effect of pentastarch, based on some previous reports. Therefore, we stopped using it. The pulmonary edema and bilateral pleural effusion due to the massive injection of normal saline solution were treated with diuretics. There was no long-term complication and no more attacks during 1 year follow-up.

Case 2

A 36 year-old female came to the hospital complaining of dyspnea and generalized edema that had started that very day. She developed upper respiratory infection 3 days before admission, but she didn't get any medication. She had a past history of 5 admissions at another hospital for the same symptoms; she underwent various examinations at that time but didn't get the proper diagnosis. She finally turned out to have SCLS at our hospital 2 years before this admission and was being followed up. She was alert and the systolic blood pressure was 40 mmHg, heart rate: 130 beats/min, respiratory rate: 30 breaths/min and a temperature of 36℃. Her breath sounds were normal. According to the laboratory finding taken on admission, her hemoglobin level was 21.1 g/dL, hematocrit: 62.7%, leukocytes: 49,700/mm^2, platelets: 297,000/mm^2, BUN/Cr: 22.6/2.7 mg/dL, total protein/albumin: 4.4/2.5 g/dL, CRP: 4.9 mg/L and CVP: 2 cmH_2O. The serum protein electrophoresis detected monoclonal gammopathy and the immunofixation test detected IgG kappa. The C1 esterase inhibitor level was normal and the bone marrow biopsy had no evidence of multiple myeloma. We started injecting 2 L of 10% pentastarch, along with inotropic drugs, instead of normal saline solution. One hour after pentastarch injection, her blood pressure began to rise and the CVP was 11 cmH_2O, but no improvements were seen in the laboratory data that was checked at that time. Later, we injected methylprednisolone, calcium, aminophylline and after that, her blood pressure didn't drop and the patient's condition gradually got better. Because she did not undergo massive fluid therapy, she did not suffer from respiratory failure resulting from pulmonary edema. During her 5 day hospital stay, the patient showed improved an hemoglobin level: 10.5 g/dL, hematocrit: 31.0%, BUN/Cr: 11.4/0.4 mg/dL and protein/albumin: 5.2/3.4 g/dL. The patient was discharged after being administered oral prednisolone and theophylline.

DISCUSSION

Systemic capillary leak syndrome is a rare condition that was discovered by Clarkson et al in 1960[1]. The prodromal symptoms are fatigue, nausea, abdominal pain and syncope. It can also present with decreased blood pressure, rhabdomyolysis, generalized edema and acute tubular necrosis-induced renal failure[2, 3]. This syndrome has two phases. The initial capillary leak phase may last 1 to 4 days and this is the essential phase of acute hypovolemia that's due to marked extravasation of intravascular fluids and macromolecules. Therefore, hemoconcentration, leukocytosis, an increased IgM concentration and a decreased concentration of albumin, IgG, C3 and C4 may occur, as well as extravasation of up to 70% of the plasma[3]. In the recruitment phase, the initially extravasated fluids and macromolecules shift into blood vessels, causing a severe acute intravascular fluid overload. The disappearance of renal shut-down and an increased urine output are the main characteristics of this stage. But fluid overload can also cause pulmonary edema, as in the case of the first patient, who suffered from pulmonary edema in the recruitment phase and she was treated by diuretics[3].

The pathogenesis of this syndrome is not yet clear. Though some of these patients have been diagnosed with multiple myeloma during follow-up, this syndrome is supposed to have something to do with monoclonal gammopathy without any evidence of multiple myeloma[3]. According to Amoura et al. among 29 SCLS patients who had monoclonal antibody, 16 people of them had IgG kappa, 6 of them had IgG lambda, 1 of them had IgA lambda, and one had mixed a form of IgG kappa and IgG lambda[4]. As seen from above, most of these patients had IgG kappa, like our own patients. Assaly et al attributed the mechanism of endothelial cell leak first to widening of the intercellular gaps resulting from increased intracellular calcium, and secondarily to endothelial cell damage and destruction. They also described apoptosis that was caused by various inflammatory responses as a mechanism of this

damage to the endothelial cells. They also emphasized the importance of IL-2, TNF-a, and leukotrien metabolites, according to the literature[5]. Considering the fact that not only our own patients, but also the ones in various reports suffered from upper respiratory infection, there's no denying that an inflammatory response is a major triggering factor for this disease.

Several trials have been done with using theophylline, diuretics, terbutaline, steroids, calcium antagonist, Ginkgo biloba extracts and plasmapheresis as medication for SCLS, yet none of them have proven to be effective[6]. Considering that this disease is self-limiting, conservative treatment in the acute phase is believed to be very important. This syndrome can be a fatal disease because cardiovascular collapse can occur in the initial capillary leak phase. Approximately one third of the cases died in the initial capillary leak phase. Therefore, fluid therapy is very important in SCLS since it reduces the mortality. Because shifting of fluid and protein by capillary hyperpermeability is the pathophysiology of this syndrome, massive crystalloid fluid therapy would not be effective during the acute attack and it exacerbates the pulmonary edema. According to Fishel et al, in case of capillary leak caused by infection or inflammation, using excessive crystalloid solution is not a good option because it could impede the oxygen supply to tissue by creating pulmonary edema, and too much normal saline could cause metabolic acidosis; therefore, using colloid solution such as albumin could be more efficient in this type of case[7]. When used with an equal amount with normal saline solution, albumin could reduce the inflammatory responses and help create an efficient oxygen supply in tissue. But albumin could be less effective if it's leaked, so pentastarch is more recommendable[7]. Though we don't exactly know how a big molecule gets out of the capillary at the acute phase of SCLS, injecting a higher molecular weight material than albumin could be effective, considering that hypoalbuminemia is present in SCLS. According to Atkinson et al, materials with a molecular weight less than 200,000 daltons can get out of the capillary[8]. Considering the fact that the mean molecular weight of Pentastarch is 264,000 daltons, injecting pentastarch as the initial fluid in the initial capillary leak stage could be efficient to prevent the cardiovascular collapse and pulmonary edema that's due to massive fluid therapy. We actually did see reduced edema and elevated blood pressure in our patients when they were supplied with 10% Pentastarch. Pentastarch has side effects such as PT prolongation. Therefore, Pentastarch could be very effective for the patients in their acute phase, but only if it's used cautiously enough to avoid a prolonged PT.

SCLS is a very rare syndrome with only 60 cases having been worldwide, and only 1 case has been reported in Korea[9]. However the incidence rates are climbing and we have experienced 2 cases in the short term. We think this indicates that SCLS could be misdiagnosed as other disease such as idiopathic edema or polycythemia vera, and so it is treated in a wrong way that could lead to death from repetitive attacks.

In conclusion, having an awareness of SCLS and effective treatment are very important. Physicians must be aware of this illness and be well prepared to treat this effectively when finding one of these patients, and the opportunity for conservative management must not be missed. Using 10% pentastarch during the acute phase of SCLS may be a key to a good prognosis and this treatment will eventually make the patients' lives better.

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