Araştırma Makalesi

Capillary Leak Syndrome: Our Clinical Experience and Literature Review

Kapiller Kaçış Sendromu: Klinik Tecrübemiz ve Literatür İncelenmesi

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Abstract

Background: Our objective is to discuss the cases of patients diagnosed with capillary leak syndrome (CLS) that is a potentially fatal and extremely rare condition, in the light of literature, and present them to clinicians' attention.

Material and Method: Six cases diagnosed with CLS between 2010 and 2016 were included in the study. The patients were diagnosed with clinical findings including hypotension (systolic blood pressure ≤90 mmHg, or a decline of ≥40 mmHg in immediate blood pressure), hemoconcentration, hypoalbuminemia (a decrease of ≥0.5 gr /dL in albumin level) and edema (local or anasarca). Information about the patients was elicited through the analysis of patient files retrospectively. The present study was carried out at the Infectious Diseases Clinic and Intensive Care Unit of Harran University Hospital.

Results: Of the six patients, three were males and three were females, and their ages ranged between 22-80. The patients' diagnoses were one patient brucellosis and one patient tuberculosis, one patient monitored in intensive care unit because of deep vein thrombosis along with pulmonary embolism and the other monitored due to hypoglycemic coma, one patient who received chemotherapy due to acute myeloid leukemia (AML), and the other one who have undergone a critical surgical intervention. Except for the patient with AML, multiple bacterial species became superposed in the patients and caused them to progress into sepsis. As all patients were intubated, culture growth was detected in deep tracheal aspirates apart from blood culture. These infections gave rise to both the development of CLS and increased mortality. All of the patients died, despite our all efforts of treatment and follow-up interventions

Conclusion: CLS remains to be a mysterious illness which is extremely rare. It still has high mortality and does not have a certain treatment. Clinician needs to be alert about the patients' progress to CLS, particularly in septic cases, because early diagnosis and treatment will turn the cycle to the favor of patients.

Keywords: Capillary leak syndrome, clinical experience, diagnosis, treatment, prognosis

Öz

Amaç: Amacımız, potansiyel olarak fatal ve oldukça nadir görülen Capillaryleaksyndrome (CLS) tanısı koyduğumuz hastaları literatür eşliğinde tartışarak klinisyenlerin dikkatine sunmaktır.

Materyal ve Metod: Çalışmaya 2010-2016 yılları arasında CLS tanısı alan6 vaka alındı. Hastaların tanısı, hipotansiyon (sistolik kan basıncı ≤90 mmHg veya mevcut kan basıncının ≥40 mmHg düşmesi), hemokonsantrasyon, hipoalbuminemi (albumin düzeyinin ≥0.5 gr /dL düşmesi) ve ödem (lokal veya anazarka tarzında) klinik bulgularıyla konuldu. Hastaların bilgileri, retrospektif hasta dosyaları incelenerek elde edildi. Bu çalışma,üniversitemiz enfeksiyon hastalıkları kliniği ve yoğun bakım ünitesinde yapıldı.

Bulgular: Hastaların üçü erkek, üçü kadın olup yaşları 22-80 arasındaydı. Hastalardan biri bruselloz, biri tüberküloz, biri derin ventrombozu ve pulmoneremboli nedeniyle yoğun bakıma alınan, biri hipoglisemik koma nedeniyle yoğun bakımda takip edilen, biri akut myeloid lösemi (AML) nedeniyle kemoterapi alan diğeri büyük cerrahi girişim uygulanan hastalardan oluşuyordu. AML hastası hariç diğer hastalarda birden fazla bakteri superpoze olarak hastaların sepsise girmelerine neden oldu. Hastaların tümü entübe edildiğinden kan kültürü yanı sıra alınan derin trakealaspiratta da üreme oldu. Bu enfeksiyonlar, hem CLS gelişmesine hem de mortaliteyle sonuçlanmasına neden oldu. Takip ve tedavi sonunda bütün çabamıza rağmen hastalarımızın tamamı exitus oldu.

Sonuç: CLS oldukça nadir, mortalitesi hala yüksek, tedavisi hala belirsiz gizemli bir hastalık olarak kalmaya devam etmektedir. Klinisyenlerin özellikle septik durumlarda hastaların CLS'ye gidişi konusunda uyanık olmaları gerekir. Zira erken tanı ve tedavi döngüyü hastanın lehine çevirecekbilecektir.

Anahtar Kelimeler: Kapiller kaçış sendromu, klinik tecrübe, tanı, tedavi, prognoz

Introduction

Capillary leak syndrome (also known as systemic capillary leak syndrome, SCLS, or Clarkson's disease) is a potentially lethal and extremely rare illness. The fluid in the circulatory system leaks between endothelial cells in the capillary veins, and passes into the interstitial space causing hypotension, hemoconcentration, hypoalbuminemia and edema. As a result of this, adequate perfusion cannot be provided for the vital organs, and organ failures occur (1). Merely about 200 cases have been diagnosed all over the world since this illness was defined by B. Clarkson in 1960 (2).

In this study, we aim to present 6 systemic capillary leak syndrome (SCLS) cases stemmed from different etiologies,and discuss them in the light of the current literature.

Material and Method

Six cases diagnosed with SCLS, and followed in Infectious Diseases Clinic and Intensive Care Unit at Harran University Hospital between 2010 and 2016 were included in the study. Diagnosis of the patients was made on the basis of the clinical findings including hypotension (systolic blood pressure ≤90 mmHg or a decline of ≥40 mmHg in immediate blood pressure), hemoconcentration, hypoalbuminemia (a decrease of ≥0.5 gr /dL in albumin level) and edema (local or anasarca). Information about the patients was elicited through the analysis of patient files retrospectively.

Findings

Three male and three female patients were included in the study. The patients' diagnoses were one patient brucellosis and one patient tuberculosis, one patient monitored in intensive care unit because of deep vein thrombosis along with pulmonary embolism and the other monitored due to hypoglycemic coma, one patient who received chemotherapy due to acute myeloid leukemia (AML), and the other one who have undergone a critical surgical intervention. Demographic features of the patients were shown in the table.

The cases and their features:

Case 1

Sixty-nine year-old male patient was hospitalized in our clinic based on complaints including difficulty in walking, backache, leg ache, cold-chill and anorexia, and he was diagnosed with recurring brucellosis. He was treated in our clinic with the diagnosis of brucellosis-related endocarditis and glomerulonephritis. Aortic insufficiency at 3/6 degree and vegetations in aortic valve were identified on his echocardiographic analysis. In blood culture, *Brucella*sps.was isolated. The patient's clinic improved with the treatment. He was discharged from our clinic

together with the suggestion of frequent follow-ups, and referred to the cardiac surgery clinic for continuing medical treatment and surgical evaluation. The patient did not accept the cardiac surgery, quitted the medical treatment after a period of time, and did not come for a routine follow-up. On his physical examination, pretibial edema was positive, body temperature was 37.2 ºC, radial pulse was 88/min., blood pressure was 130/80 mmHg, murmurs at 4/6 degree were heard in the aortic area, and also at 2-3/6 degree in other areas. In the laboratory analysis, brucellosis Wright test was positive at 1/640 titer, and was measured as positive at 1/320 titer with 2-mercaptoethanol test. In his hemogram, white blood cell (WBC) was 10800/mm^3, Hb was 12.4 g/dL, platelet was 102000/mm^3; in the analysis of his biochemical tests, C-reactive protein (CRP) was 11.4 (normal 0.1-0.5), urea was 71 mg/dL, creatinine was 1.9 mg/dL, albumin was 2.5 g/dL, prothrombin time (PT) was 14 sec. (normal 10-15), INR was 1.2 (normal 0.8-1.22). Serological tests for viral hepatitis A, B, C, E, toxoplasmosis, infectious mononucleosis, herpes simplex virus, cytomegalovirus and human immunodeficiency virus, blood film for malaria, salmonella agglutination tests, and tuberculin test results were negative. Blood cultures were taken and brucellosis treatment was started again. 1 unit of albumin was given due to low albumin values (2.5 g/dL). When thrombocytes began to decrease (68000/mm^3), a unit of thrombocyte was given. There was no noticeable improvement in the patient's clinic with medical treatment. When free fluid was detected in the abdomen, furosemide was added to the treatment. The patient's thrombocytes and albumin began to decrease; meanwhile his creatinine began to increase (3.37 mg/dL). In the following few days, another 4 units of albumin was given. His albumin values increased to the degree of 3 g/dL. On his 14th day in the clinic, acute respiratory distress and coughing started. At the same time, edema began to occur in the

patient's abdomen and chest. His blood pressure decreased to 100/70 mmHg. Bilateral pleural effusion and acute pulmonary edema were detected, and the patient was admitted to the intensive care unit. Salbutamol, ipratropium and steroid were commenced to the patient. The dose of furosemide was increased in order to solve edema. The analysis of fluid taken through thoracentesis revealed large amount of leucocytes and the Wright test which was studied from thoracentesis fluid was evaluated as positive at 1/1280 titer. Serum Wright test studied simultaneously was also observed to increase to 1/1280. On the following day, edema increased in the patient's whole body and took the form of anasarca. The patient's laboratory values deteriorated. WBC, Hb, thrombocyte and albumin levels decreased to 6900/mm^3, 9.4 g/dL, 51500/mm^3 and 2g/dL, respectively. Urea was 108 mg/dL, while creatinine was found to be 3.37 mg/dL, PT 26 sec. (normal 10-15), fibrinogen 67 mg/dL (normal 150-400) and d-dimer 2.05 ug/mL (normal 0-0.4). The patient was diagnosed with DIC, and a total of 15 units of FFP were given in 3 days. While he was in the intensive care unit, hallucination and confusion (SCLS-related cerebral edema) began. Though two units of albumin were given, the albumin level didn't increase over 2g/dL. The patient's edema continued in the anasarca form. Fresh frozen plasma (FFP) was continued to be infused because PT and aPTT continued to increase. Failing to respond the treatment, the patient remained unresponsive to the treatment, and eventually progressed into anuria. The patient having anasarca, bilateral pleural effusion, acute pulmonary edema and abdominal fluid was diagnosed as brucellosis-related SCLS. On the following day, he was connected to the mechanical ventilation device upon the development of cardiopulmonary collapse, and the next day died.

Case 2:

The patient was a 25-year-old Syrian male. He was admitted to our clinic with complaints of headache, fever, mental fog, and with the findings of neck stiffness, Kerning and Brudzinski positivity. In his laboratory analysis, white blood cell count was 6000 /mm^3, Hb was 14gr/dL, Platelet was 144000 /mm^3, albumin was 3.5 g/dL, and other laboratory tests were normal. In lumbar puncture, the pressure was high, the color was xanthochromic, the leukocyte was 690 (90% lymphocyte), protein was 231 mg/dL, and CSF/Blood glucose ratio was 3/107. Anti-Tuberculosis (Tb) treatment via NG was started immediately, but the patient did not regain consciousness. Since Methicillin Resistant *Staphylococcus epidermidis* growth was detected in CSF cultures on the following day, vancomycin was added to the treatment. Hydrocephaly was detected on brain MRI. On the 7th day of the treatment, aspiration pneumonia and atelectasis developed. Lungs were cleaned through bronchoscopy and re-aspiration. After two weeks of the treatment, colistin was added due to *Acinetobacter baumannii*growth in the tracheal aspirates. PCR analysis of CSF for *Micobacterium tuberculosis* (MTb) DNA was found to be positive, and CSF ADA was 25 IU/ml. Vancomycin and colistin were continued by the end of the 3rd week. On the 35th day of the Anti-Tb treatment, maculopapular rash and fever developed. Hepatomegaly (210 mm) and splenomegaly were detected on ultrasonographic examination, and granulomatous hepatitis was diagnosed in liver biopsy. Linezolid was added because of the vancomycin resistant *Enterococcus* (VRE) growth in the cultures taken from the decubitus ulcers which occurred sporadically. After two months of treatment, the patient regained consciousness, his decubitus wounds recovered, fever reduced and his general condition improved. The patient who was accompanied by sustained conditions including right facial paralysis, fecal and urinary incontinence and partial hydrocephaly

was discharged from the clinic with isoniazid (INH) and Rifampicin.

The patient was brought to the clinic for a follow up visit two months later, because of the recurring fever, swelling in his abdomen and extremities beginning while he was in Syria. He declared that he had stopped taking his medicine several weeks ago. Capillary leak syndrome was considered in the patient based on the laboratory and clinical findings including pancytopenia (WBC 2900/mm^3, Hb-7.9 gr/dL, platelet 21000 /mm^3), hypotension (90/60 mmHg), hypoalbuminemia (1.7 gr/dL), fever and widespread edema, and the treatment was commenced again. Fluid began to leak from both of his legs. Additionally, pleural and pericardial effusions were diagnosed on his radiological analysis. Platelet counts and Hb level decreased to 11000 / mm^3 and 6.5 gr/dL, respectively. When respiratory distress occurred, the patient was intubated.

At the end of our treatment efforts lasting for 4 months and 12 days, the patient with Tb meningitis and multiple organ involvement, aspiration pneumonia-atelectasis, several secondary bacterial infections and eventually SCLS became exitus due to cardiopulmonary collapse.

Case 3:

The 80-year-old, female patient was hospitalized in our clinic with the diagnosis of acute cholecystitis. According to her history, she had undergone right sciatic surgery 10 days ago. On her physical examination, her body temperature was 37 ºC, radial pulse was 85/minute, blood pressure was 130/80 mmHg. In her laboratory analysis, white blood cell (WBC) was 17100/mm^3, Hb was 9.6 g/dL, platelet was 192000/mm^3, C-reactive protein(CRP) was 8.4 mg/dL (normal 0.1-0.5), urea was 63 mg/dL, creatinine was 1.2 mg/dL, albumin was 3.1 g/dL, PT was 13.7 sec. (normal 10-15), and INR was 1.09 (normal 0.8-1.22). After her admission, the

patient's oral intake was stopped, and ceftriaxone and metronidazole were commenced. On radiological and laboratory analysis performed upon her complaint of shortness of breath, the patient was diagnosed with pulmonary emboli and deep vein thrombosis. Upon the beginning of respiratory distress, the patient was intubated. As *Acinetobacter baumannii*was grown in deep tracheal aspirates and blood cultures after a few days, imipenem and colistin were started. Two units of albumin were given because the serum albumin level decreased to 2 g/dlL Anasarca edema began to be observed in the patient. Despite albumin support, her serum albumin level decreased to 1.59 g/dL. Although the patient was given 2 units of albumin again, her albumin level did not increase at all. The patient's whole body swelled and fluid began to leak from the edemas at the dorsum of her hands and legs. The patient's body temperature fell to hypotermic level (32 ºC) on the following days. As being unresponsive to antibiotic, albumin, inotropic support, fluid and other support treatments, the patient developed cardiopulmonary collapse and became exitus in a few days.

Case 4:

A 77-year-old female patient was admitted to the ICU due to hypoglycemic coma (blood glucose level of 10mg/dL). In her medical history, type 2 diabetes for 20 years, hypertension, chronic renal failure, surgical operation (prosthesis in the knee and waist), and coronary artery disease were present. Detailed physical examination revealed that the patient's general condition was poor, and she was unconscious. Her blood pressure was 150/90 mmHg, radial pulse was 82/minute with normal rhythm, albumin was 3.3 g/dL, and body temperature was 36.8 ºC. Her medical history clued the development of perspiration and mental fog following insulin injection at home. WBC was 17000/mm^3, Hb was 7g/dL, platelet was 549000/mm^3, and Htc was 23. Upon detecting *Klebsiella pneumonia*

growth in her urine cultures a few days later, ertapenem was started. Two days later, hypoalbuminemia (1.8 g/dL), hypotension (90/60 mmHg) and edema developed. Dopamine was started and the patient was given two units of albumin. As MRSA growth was identified in her blood cultures during the follow-up, teicoplanin was added to the treatment. After one week, 2 additional units of albumin were consecutively given upon a critical decrease of her albumin level. The patient's blood pressure was 110/70 mmHg, and her albumin was 2.6 mg/dL. On the following day, edema occurring in the patient's pretibial area began to spread to the dorsum of her hands. Four days later, her blood pressure was 90/50 mmHg, albumin was 2.3g/dL, body temperature was 38 ºC, and radial pulse was 80/min. Although dopamine and albumin were given, her blood pressure and albumin level did not increase; in contrast, persistently continued to decline. The local edema took the form of anasarca as it spread to the whole body. Her blood pressure was measured to be 70/40 mmHg, radial pulse 90/min., albumin 1.8 g/dL, and fever 38.7 ºC. She died despite all efforts, because she did not respond to dopamine, albumin, antibiotic, fluid support and other supportive treatments.

Case 5:

The 57-year-old male patient was taking chemotherapy due to diagnosis of acute myeloid leukemia (AML). He was hospitalized because he was refractory to the treatment. The patient was given FLAG (Fludarabin, Ara-C ve G-CSF) treatment. His vital findings were stable, albumin was 3 g/dL, WBC was 41/mm^3, neutrophil was 35/mm^3, Hb was 8.2 g/dL, and platelet was 3800/mm^3. On the following day, the patient's blood pressure declined (75/40 mmHg). Urination of the patient decreased. Serum AST level was 439 IU/L, ALT was 273 IU/L, creatinine was 2 mg/dL, urea was 85 mg/dL, total bilirubin was

4.7 mg/dL, and albumin was 2.8 g/dL. Noradrenalin infusion was commenced. One day later, his urination ceased completely. The patient's general condition further deteriorated on the following day, and he lost his consciousness. 3 units of fresh frozen plasma (FFP) and thrombocyte were given to the patient whose blood pressure was 95/55 mmHg, body temperature was 38.5 ºC, INR was 2.4 and platelet was 9000/ mm^3. Upon worsening in respiration, the patient was intubated. His arterial blood pressure could hardly be held at 100/50 mmHg level through adrenalin infusion. Two days later, the patient's biochemistry parameters showed that urea was 268 mg/dL, creatinine was 3 mg/dL, AST was 175 IU/L, ALT was 751 IU/L, total bilirubin was 24 mg/dL, albumin was 2.6 g/dL, and CRP was 26 mg/dL. The patient's arms and limbs began to swell; on the following day, the edema advanced and turned out to be anasarca-type on his whole body. His general condition was poor, he was unconscious and intubated, and his blood pressure was 90/60 mmHg despite dopamine and noradrenalin infusions. Urea turned out to be 268 mg/dL while creatinine became 3 mg/dL, AST 175 IU/L, ALT 751 IU/L, total billirubin 25 mg/dL, albumin 2 g/dL, Na 147mEq/L, and CRP 26 mg/dL. The general condition of the patient, whose widespread anasarca-type body edema continued, deteriorated and he became exitus. He could not be rescued despite all interventions.

Case 6:

The patient was a 22-year-old female. On the physical examination of the patient who was hospitalized with acute upper gastrointestinal bleeding, the general condition was bad; she was unconscious, cooperative and oriented.Her blood pressure was 135/75 mmHg, radial pulse was 87/min. and body temperature was 36.3 ºC. In her laboratory findings, WBC was 8000/mm^3, Hb was 7.6/g/dL, platelet was 182000/mm^3, albumin was 2.3 g/dL, AST was 275 IU/L, ALT was 195 IU/L, GGT was 609 IU/L, ALP was 459

IU/L, and CRP was 5 mg/dL. The patient was intubated because respiration distress started. The patient was given 16 units of FFP and 15 units of erythrocyte suspension. Two days later, the patient who was urgently taken to operation due to unceasing gastrointestinal hemorrhage underwent total gastrectomy. Her general postoperative condition was poor with tachycardia and hypotension. In her blood cultures and deep tracheal aspirates, *Acinetobacter baumannii* was grown, and *Candida albicans* was grown from the tip of the drains. There was serohemorrhagic fluid from the drains. The patient was given FFP and erythrocyte suspension support again. The patient's albumin and blood pressure began to decrease (albumin. 1.6 g/dL, blood pressure 90/65 mmHg). Although sufficient blood transfusion and albumin support were provided, blood pressure and albumin level continued to keep low. Swellings started in his extremities, abdomen and face. The patient was applied dopamine and noradrenalin treatment. On the following days, abdomen distension advanced and anuria developed. His abdomen was re-opened surgically; there was light intraabdominal hemorrhage. It was aspirated and homeostasis support was provided, the skin was closed after changing the patient's abdominal drains. Despite fluid and albumin support, blood pressure and albumin did not increase. WBC was 1700/mm^3, Hb was 6.7g/dLmm^3, platelet was 22000/mm^3, urea was 101 g/dL, creatinin was 2.4 g/dL, and CRP was 37 g/dL. The patient whose general condition deteriorated on the 7th postoperative day became arrest in spite of all supportive treatments. The patient who could not be revived despite resuscitation was considered as exitus.

Discussion:

Capillary leak syndrome may basically occur due to 1) idiopathic, 2) autoimmune and 3) secondary reasons. SCLS occurs secondarily resulting generally from infections (fungal, viral, bacterial), malign diseases (lymphoma, hematologic cancers, solid organ cancers),

trauma (surgical applications and other traumas), and therapeutic agents (chemotherapy agents, growth factors, other agents) (3,4).

Pathogenesis and Prognosis: As capillary leak syndrome commonly presented by sporadic cases, it is quite difficult to analyze its physiopathology, and thus its molecular pathogenesis cannot be highlighted. It is pointed out that other etiological factors, in particular infection,disrupts the autoimmune system eventually causing capillary extravasation, organ failures and subsequent complications developed due to fluid reduction in the veins. As a result of this process, arrest and exitus occur due to cardiopulmonary collapse. It is clear that a factor or factors in blood initiating capillary extravasation give rise to the development of these events, but it is not precisely clear what these factors are. Depending on whether the etiology of the disease stems from idiopathic, autoimmune, infectious or other reasons, the factors taking a role in the physiopathology will show variance. In a study, it was reported that CXCL10, CCL2, IL-1β, IL-6, IL-8, IL-12 and TNFα increased during acute phase (4-8). Monoclonal gammopahty often accompanies the syndrome, but its importance in the physiopathology is not known yet (9). Some authors expressed that genetic tendency might be responsible (10).It is acknowledged that infection and inflammation starts acute SCLS episode by triggering proinflammatory factors (11).Depending on the course of prognosis in SCLS developed subsequent to common infections, it was explicated that mortality ratewas 34%, while the mortality increased to 80% in cases that were serious enough to be followed in intensive care units (12,13).

Treatment:Apart from the seriousness of the syndrome, there is no clear-cut treatment for it. Occurring the disease in connection with different etiologies plays a role as a factor complicating the treatment. Although positive

results have been recentlyachieved in some patients through various treatments applied at case level, the majority remains inconclusive. It is also not clear how successful the applied treatments are. The main treatment at the acute phase includes fluid replacement and administration of albumin. If needed, inotropic infusion and supportive care should be given. However, if the infection develops secondarily, initiation of antibiotics is of priority in the treatment (12, 14).

Other treatments that have been recently tried out and yielded positive results in some cases in the acute phase include: beta agonists such as terbutaline, phosphodiesterase inhibitor theophylline and leukotriene receptor antagonistsmontelukast sodium andin addition to Epoprostenol, Infliximab, plasmapheresis. Meitanence; IVIG, Theophylline plus terbutaline, and corticosteroids (15-17).

Differential Diagnosis:Even though SCLS is clinically similar to toxic shock syndrome and sepsis syndrome, these syndromes differ from SCLS as the albumin level in both cases is normal. In the nephritic syndrome, however, hypoalbuminemia also accompanies the condition in addition to similar clinical picture. Yet the definitive feature here is that proteinuria exists whena renal pathology is present. In SCLS, however, the pathology is not renal; it is in capillary endothelium cells, thus SCLS and nephrotic syndrome differ from one another (2.12).

Scrutinizing Our Cases:

Two of our cases were infection-originated (Table, Case 1 was brucellosis and Case 2 was tuberculosis). In two cases (Cases 3 and 4), infection developed secondarily. Case 5 was taking chemotherapy due to AML and Case 6 comprised the patient who had a major operation and superimposed infection.Brucellosis-related SCLS is quite rare and very few cases have been reported (18). Except for hemoconcentration, a clinical picture of SCLS was present in our case. The

reason for the absence of hemoconcentration is that brucellosis progresses with cytopenia as a characteristic of the disease. Brucellosis causes cytopenia by suppressing either the shaped blood elements in blood or bone marrow (19). In the first case of SCLS brucellosis reported in 2008, also pancytopenia had developed instead ofhemoconcentration (18). Occurrence of relapse due to noncompliance with treatment, presence of endocarditis accompanying it and having hypertensionhistory played a facilitating role in our case. With the progress of the disease in our case, fluid extravasation into visceral organ ventricles, subsequently renal failure and cardiopulmonary collapse developed.

As far as we know, no tuberculosis-related SCLS case has been reported until now. In this regard, our patient is the first reported case. In our case, the development of SCLS was facilitated because our patient had other organ involvement (lung, liver, spleen) in addition to tuberculosis meningitis and several secondary bacterial infections.Additionallythe development of resistance to tuberculosis bacillus was present probably due to the patient's noncompliance with the treatment. Eventually, advanced thrombocytopenia and also cytopenia in other shaped blood elements, hypotension, hypoalbuminemia, fluid extravasation into visceral organ ventricles, fluid leakage from the legs and subsequently cardiopulmonary collapse developed.The patient who was admitted for acute cholecystitis and diagnosed with pulmonary emboli, deep vein thrombosis and respiratory distress was taken to intensive care and intubated. We assume that the patient's immobility due to having a sciatic operation ten days earlier laid the ground for emboli. No response could be achieved to the treatment that was started upon *Acinetobacter baumannii*growth in deep tracheal aspirate culture and also blood culture which were taken during follow-up in

intensive care unit. Blood pressure and albumin declined dramatically. Blood pressure became 90/50mmHg and albumin became 1.59 g/dL. Hypothermia (32 ºC) and cytopenia developed in the patient. Fluid leakage started at the dorsum of the hand in spite of antibiotic, albumin, fluid, inotropic and other supportive treatments. The patient developed cardiopulmonary collapse and became exitus.We think that SCLS developed as a result of the serious infection in addition to the advanced age (80),undergoing a severe operationand several accompanied medical disorders.

The patient who was admitted to the intensive care unit due to hypoglycemic coma (glucose 10mg/dl)) revealed a combination of diabetes mellitus for 20 years, hypertension, chronic renal failure, coronary artery disease and advanced age (77). During follow-up in intensive care unit,MRSA (Methicillin Resistant *Staphylococcus aureus*)was grown in her blood culture and *Klebsiella pneumonia*in her urine culture. While the treatment was being continued,clinical picture of SCLS developed and the patient became exitus. The patient's advanced age was and having several additional diseases played a role as facilitating factors for SCLS.

A number of caseswith development of SCLS, as a result of chemotherapy application were reported in patients with malign conditions. Zhang F *et al*. indicated that capillary leak syndrome developed in a patient with breast cancer as a result ofTrastuzumabadministration (20). Pothen L *et al*. documented capillary leak syndrome d in a patient with diffuse large B-cell lymphoma (21),and similarly Durand D.M. *et al*. reported development of capillary leak syndrome in a patient with Chronic Lymphocytic Leukemia (22). Also, Anderson BJ *et al*. found that SCLS developed in a patient taking oxaliplatin due to colon cancer (23). Our patient had acute myeloid leukemia refractory to treatment. The

patient who was taken for follow-up was started FLAG (Fludarabin, Ara-C and G-CSF) treatment. Following the treatment, capillary leak syndrome developed within seven days, and the patient became exitus.

Ozawa T *et al*. reported the first case of capillary leak syndrome which developed secondarily at the end of an abdomino-perineal resection (24). Our patient is the second case in which capillary leak syndrome developed as a result of a surgical procedure. Apart from the major surgical operation conducted in our case, the addition of hemorrhage and secondary infection caused the patient to be exitus.Whereas mortality was found to be 80% even in serious cases published so far (12, 13), it was observed to be 100% in our patients. We believe that the main reason for this finding was that all our patients but the patient with AML had serious infections apart from having several diseases simultaneously. It is the fact that the first two cases in the Table were complicated with other bacterial infections carrying antimicrobial resistancealong with multiple organ involvement. The following two cases harbored a few acute and chronic diseases together in addition to their advanced ages. The fifth case had refractory AML in which poor prognosis and SCLS were superimposed as a characteristic of the disease.The last case had SCLS in addition to major surgical operation, hemorrhage at an advanced leveland complicated resistant infections ended in mortality.

The absence of hemoconcentration in our cases can be explained by hypothermia occurring in patients who developed severe sepsis due to infection and suppression of the bone marrow. Actually, hypothermia and cytopenia are expected at advanced stages when sepsis becomes severe (25).Capillary leak syndrome remains to be a mysterious illness which is extremely rare and thus has a vague physiopathology. It still has high mortality and does not have a certain

treatment. Physician needs to be alert about the patients' progress to CLS, particularly in septic cases, because early diagnosis and treatment will turn the cycle to the favor of patients. In the cases we depicted above, although we were unsuccessful in treatment, which was a result of the disease itself and the complicated situations accompanying it, we tried to present our experiences by drawing attention to infection-related SCLS cases.

Conclusion, despite the developments in medical science and technology, SCLS continues to challenge the medical world with the obscurity of its physiopathogenesis, uncertainty of its treatment and high fatality. It appears that we have a long way to go in this regard.

Table: The demographic features and laboratory findings of patients

P	Year	Sex	PrimerDisease	Albumin[1] **Albumin[2]**	Blood Pressur[1] **Blood Pressur[2]**	Edema[1] **Edema[2]**
1	69	M	Brucellosis Endocarditis	3 gr/dL **2** gr/dL	130/80mmHg **80/40**mmHg	Yes (+)/ anazarka
2	25	M	TuberculousMeningitis	3.5 gr/dL **1.7** gr/dL	120/80mmHg **90/60**mmHg	No/ anazarka
3	80	F	AcuteCholecystitis, DVT, PE	3.1 gr/dL **1.59** gr/dL	130/80mmHg **90/50**mmHg	No/ anazarka
4	77	F	HypoglisemicComa CRF, CAD, HT	3.3 gr/dL **1.8** gr/dL	150/90mmHg **70/40**mmHg	No/ anazarka
5	57	M	AML+CT	3 gr/dL **2** gr/dL	? **60/40**mmHg	No/ anazarka
6	22	F	MajorOperation	2.3 gr/dL **1.6** gr/dL	130/75mmHg **60/40**mmHg	No/ anazarka

Abbreviations

P:*Patients*	*Albumin[1]: pre SCLS*	***AML:****Acutemyeloidleukemia*
DVT*: Deepveinthrombosis*	***Albumin[2]:****SCLS*	***HT****: Hypertension*
PE*: Pulmonaryembolism*	*Blood Pressur[1]: pre SCLS*	***CAD****: Coronaryarterydisease*
CRF*: Chronicrenalfailure*	***Blood Pressur[2]:*** *SCLS*	***CT****: Chemotherapy*
M*: Male*		***F****: Female*

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