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Refractory Hyponatremia due to Systemic Infection: A Systematic Review

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ABSTRACT

Introduction: Hyponatremia is a condition in which the sodium serum level is below the normal range. This condition is most common in hospitalized patients receiving systemic infection therapy and can lead to worse outcomes, potentially life-threatening. **Objective:** This study aimed to summarize the incidence of refractory hyponatremia due to systemic infection therapy. **Methods:** This was a systematic literature search conducted in October 2023 on the online database PubMed regarding refractory hyponatremia due to systemic. The analysis excluded narrative reviews, non-English studies, and studies that only discussed transient hyponatremia or local infections. **Results:** A total of 10 case reports of 11 patients were included in the final analysis. The mean age of patients was 46.63 years (SD = 20.79 years), and 63.64% were male. Strongloides stercoralis hyperinfection was the most common cause of systemic infection (54%). It was followed by disseminated Varicella-zoster virus infection (28%), tuberculosis (9%), and systemic nocardiosis (9%). The most common cause of immune compromise is stem cell transplant recipients (28%), followed by miliary tuberculosis (18%). Up to 91% of cases are caused by the syndrome of inappropriate antidiuretic hormone (SIADH), which is the pathophysiology of hyponatremia. **Conclusion:** Most patients with systemic infections and refractory hyponatremia have conditions that encourage immune compromise. The treatment of systemic infections is a priority since they contribute to hyponatremia.

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INTRODUCTION

Electrolytes play a role in the normal conduction function of body cells. Electrolytes contain ions such as sodium, potassium, calcium, phosphorus, and magnesium, all of which play a key role in maintaining body homeostasis.[1] Sodium ions, as extracellular fluid cations, are an electrolyte that helps to maintain the normal distribution of water and osmotic pressure in body fluids. Hyponatremia is an electrolyte balance disorder that frequently occurs in hospitalized patients, with a prevalence of 15–40%.[2]

Hyponatremia is defined as having a serum sodium level of ≤135 mEq/l.[3] Aside from being the most common electrolyte balance disorder, hyponatremia can lead to life-threatening complications.[4] Acute hypotonic hyponatremia, occurring in less than 48 hours, can cause cerebral edema, which manifests as decreased volume status in cases of gastrointestinal losses, adrenal insufficiency, or cerebral salt wasting syndrome (CSWS), volume status expansion in cases of heart failure and liver cirrhosis, and syndrome of inappropriate antidiuretic hormone secretion (SIADH) in normal volume status.[5]

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common cause of hyponatremia. SIADH happens when the body releases the antidiuretic hormone (ADH) without being properly stimulated. This leads to hypotonic and euvolemic hyponatremia, as well as high osmolality in the urine.[3] In addition, infections are known to contribute to the incidence of hyponatremia, and conversely, hyponatremia is associated with prolonged hospitalization, poor outcomes, and higher mortality rates in patients with infections. Hyponatremia may also play a diagnostic role in distinguishing the pathogen causing a particular infection.[6] Several studies have discussed hyponatremia in patients with infectious disease.[6,7] As far as the author knows, there has been no systematic analysis of the relationship between systemic infections and refractory hyponatremia, which is associated with high mortality and difficult treatment. Therefore, in this article, the author would like to summarize refractory hyponatremia due to systemic infection.

OBJECTIVE

This study aimed to conduct a systematic review of case reports on refractory hyponatremia due to systemic infection.

METHODS

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplement 1) and is registered in the PROSPERO online database (PROSPERO Identifier: CRD42021256746). A systematic literature search regarding refractory hyponatremia due to systemic infections was carried out on the online database PubMed in October 2023. The search used a combination of keywords: "*refractory hyponatremia*" or "*relapsed hyponatremia*" or "*recurrent hyponatremia*" or "*resistant hyponatremia*" or "*intractable hyponatremia*" or "*persistent hyponatremia*" or "*permanent hyponatremia*" or "*syndrome of inappropriate antidiuretic hormone*" or "*systemic infection*" or "*viremia*" or "*bacteremia*" or "*parasitemia*" or "sepsis." The analysis excluded narrative reviews, non-English studies, and studies that only discussed transient hyponatremia or local infections.

Screening and data extraction were performed independently by the authors. All studies discovered through the literature search were screened against the title and abstract to determine the study's relevance. Studies deemed relevant through the screening were then subjected to full-text review. After a full-text review, studies that were deemed relevant were included in the final analysis. Figure 1 shows the PRISMA 2020 reference search and collection flowchart. All studies (n = 10) were case reports of 11 patients suspected of having refractory hyponatremia due to a systemic infection.

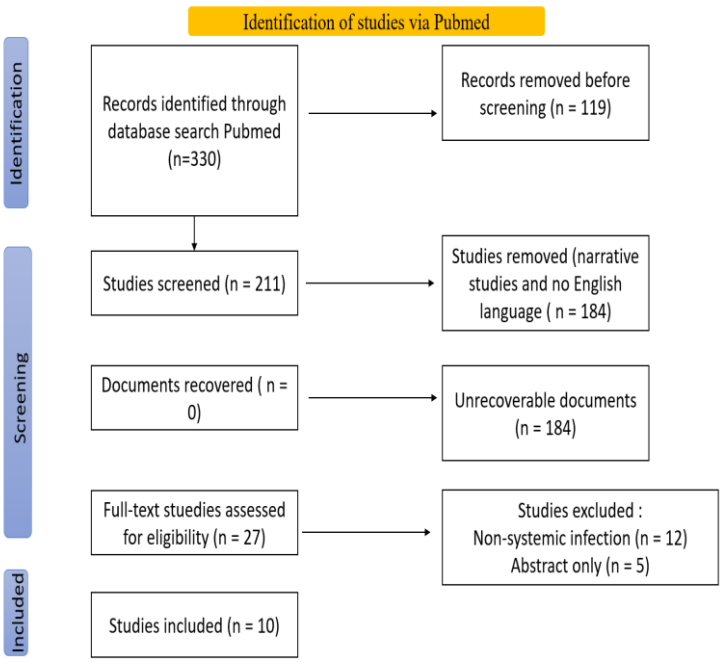

Figure 1. Flowchart of PRISMA 2020 referance search and collection

RESULTS

Table 1. Case report

Researcher, year	Gender, age	Clinical Presentation	Comorbid	Laboratory	Imaging	Diagnosis	Therapy	Outputs
Arzuaga et al. 1994[8]	Male, 43 years old,	Right abdominal and lumbar pain, stupor on the 13th day of treatment, urinary incontinence, and multiple erythema papules with vesicles primarily in the right abdomen and lumbar region, with a discrete spread in the lower extremities.	- History of *chicken pox* infection in childhood - HIV positive with heterosexual route of transmission since a year ago	- Pansitopenia - Hyponatremia - Urine culture (-), blood culture (-), stool culture (-) - Stool microscopy (-) - BTA urine sample (-), feces (-), culture (-) - BTA culture (-) - Bone marrow smear: diffuse hypocellular tissue without parasitic or granulomatous involvement - CSF: clear, 1 cell/dl, glucose 50 mg/dl, protein 92 mg/dl - Adenosine deamination <5 u/ml - Cryptococcal antigen (-) - ELISA anti HVZ antibody (+)	- CT head: diffuse cortical-subcortical retraction and dilatation of the ventricular system without focal lesions - BNO, CXR, barium enema: normal - Abdominal ultrasound and CT: normal - IV urography: *sponge kidney*	- Disseminated varicella zoster infection - SIADH - AIDS - Oral candidiasis - Pansitopenia - HIVassociated dementia	- Fluid restriction - Hypertonic saline infusion - Asiklorvir IV starting dose 750 mg/8 hours for 8 days - Cotrimocasol, zidovudin, ketoconazole, ciprofloxacin	Hospital discharge on day 26, pain and skin lesions disappeared completely.
Au et al. 2003[9]	Male, 38 years old	Severe abdominal pain with recurrent vomiting and ileus, diffuse skin lesions.	- Chronic myelobastic leukemia, has received donor allogeneic *stem cell transplantation* (SCT), patient and donor are VZV antibody positive, history of *graft versus*	- Pansitopenia - Severe hyponatremia - Immunofluorescence to VZV antigen of skin biopsy and swab samples: (+) - Lumbar puncture	Head MRI: encephalitis or hypophysitis (-)	- Disseminated varicella zoster infection - SIADH - CML on SCT	- IV acyclovir or valacyclovir and *intravenous immunoglobulin* (IVIG) - Tyrosine kinase inhibitor therapy for *blast* relapse	Complete resolution of VZV infection on day 10, complete remission of leukemia after 4 months

				and CSF analysis: Acellular CSF, high protein, VZV positive by PCR - Bone marrow				
Au et al. 2003[9]	Female, 32 years old	Abdominal pain with ileus, disseminated zoster eruption	Acute lymphoblastic leukemia and receiving a matched sib allogeneic SCT, with both donor and recipient positive for VZV antibody.	- Hyponatremia - VZV antigen: positive	Plain photograph of abdomen: ileus	- Disseminated varicella zoster infection - SIADH - AML on SCT	- Acyclovir IV 500 mg/8 h for 5 days followed by valacyclovir pO 1 g/8 h for 7 days and intravenous immunoglobulin (IVIG) single dose 0.4 g/kg - Tyrosine kinase inhibitor therapy for blast relapse	Complete resolution in 1 month
Dass et al. 2003[10]	Male, 12 years old	Polyuria, hypertension, decreased consciousness, poor perfusion, hypotension, low CVP	Tuberculosis meningitis and hydrocephalus with VP shunt and OAT (anti-tuberculosis drugs).	- Hyponatremia - Excretion of high concentrations of sodium in the urine.	CT scan of the head: gross hydrocephalus	- Tuberculous meningitis and hydrocephalus - Cerebral salt wasting syndrome (CSWS) - Shock sepsis	- Correction with 3% saline 5 ml/kg followed by 0.9% saline 2ml/kg/hour Shock management: - fluid bolus with inotropic support (dopamine 20 mcg/kg/min and dobutamine 20 mcg/kg/min - vancomycin 15 mg/kg/6 hours and cefoperazone 200 mg/kg/day CSWS Therapy: - NS fluid therapy and Fludrocortisone 10 mcg/kg/hour - Revision ventriculoperitoneal shunt + antibiotics	CVP increased, hyponatremia and GCS improved until day 10 of treatment

							(cloxacillin 200 mg/kg/day, amikacin 7.5 mg/kg/8 hours and cefotaxime 200 mg/kg/day) OAT regimen: - Isoniazid 5 mg/kg/day - Rifampicin 10 mg/kg/day - Pyrazinamide 25 mg/kg/day - Ethambutol 15 mg/kg/day	
Ohara et al. 2007[11]	Female, 65 years old	Severe abdominal pain for 2 days. Vesicular skin lesions appeared on the abdominal wall on the 6th day of treatment.	- History of non-Hodgkin lymphoma (NHL)/diffuse large B cell lymphoma post chemotherapy 2 months ago (3 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP)), followed by radiation with a total of 40.5 Gray, complete response	- Hyponatremia - Mild liver injury (SGOT 74 U/L; and SGPT 63 U/L) - Serum osmolarity = 262 mOsm/kg - Osmolarity of urine = 532 mOsm/kg, - HIVnegative - PCR for VZV from peripheral blood and CSF positive - CD4+ count = 191/L	MRI = normal pituitary gland size, but the occipital lobe of the cerebrum shows hyperintensity	- Disseminated varicella zoster infection - SIADH	- Fluid restriction - Acyclovir 1500 mg/day	The patient was discharged after 14 days, skin lesions healed, NHL went into complete remission
Chowdhury et al. 2014[12]	Male, 76 years old	Persistent vomiting, *fatigue*, nausea, weight loss of 30 pounds over 2 months, Hispanic race There is purpura and mild epigastric pain	- History of migration from the United States from Colombia 17 years ago and travelled to Venezuela 1 month ago - ITP diagnosed 4 months ago, treated with 3 weeks of steroids - Smoked 1 pack/day	- Hyponatremia - Leukocytosis - Hypoalbumin and hypo protein - HIV and HTLV negative - EGD biopsy: acute and chronic duodenitis with obvious *blunting of* villi and	EGD: erythema of the stomach and duodenum	- S. stercoralis hyperinfection - SIADH	- Ivermectin 2 12 mg dose (200 µg/kilogram) - Normal saline - Fluid restriction	Sodium increased with fluid restriction, 2 weeks after ivermectin therapy, parasites (-)

			for 40 years	reactive cellular changes, active gastritis and presence of parasites consistent with S. stercoralis - Stool examination: many S. stercoralis larvae				
Mutreja et al. 2015[13]	Male, 36 years old	Vomiting (2-3 days, non-projectile, 6-8x/day), abdominal pain (1 day, acute, continuous, moderate, epigastric, radiating -), significant weight loss (12 kg, with *general weakness*, anorexia for 1 month), malnutrition. Appears sick, thin, fever (-), pale, bilateral *pitting* edema pedis, BMI 16.3, NTE (+) mass (-), hypotension (4th day)	- Multidrug therapy for lepromatous leprosy and history of steroid therapy (prednisolone 50 mg/day and thalidomide) for type 2 leprosy reaction since a year ago.	- Persistent hyponatremia - Recurrent hypoglycaemia - Hypoalbuminemia - Hypercholesterolemia - Hypertriglyceridemia - Normocytic, normochromic mild anemia - UL = protein +, - PT and APTT lengthwise - Serum bilirubin and LDH increased - C-reactive protein positive. (H-3) - HIV, hepatitis B and C negative - Blood culture (-) - Blood gas analysis: severe metabolic acidosis. - Ascites fluid analysis: neutrophil dominant with exudate fluid	- Abdominal ultrasound: mild ascites, *free fluid* subdiaphragmatic, paraaortic, hepatic, and pelvic, *distended* gallbladder with *sludge.* - *upper gastrointestinal* (GI) *endoscopy*: gastric mucosa is fragile and erythema with yellowish deposits. - Contrast enhanced CT (CECT) abdomen: ascites, concentric thickening of the cecum, ileocecal wall and terminal ileum, impression of ileocecal tuberculosis	- S stercoralis hyperinfection with sepsis and multiple organ failure (MODS), - adrenal haemorrhage - SIADH	- Normal saline 1 L/day - Salt per oral 5 g, 6 hours - Antacids - Antiemetics	Patient died on day 4 of admission due to sepsis and MODS

Khushman et al. 2017[14]	Male, 68 years old	Heartburn, nausea, and vomiting 4 months after SCT with suspected GVHD	- Colombian citizen who lived in Miami for 17 years - *Philadelphia chromosome positive B-cell acute lymphocytic leukemia* (ALL) in December 2012, treated with hyper CVAD chemotherapy and imanitib□ remission□ *matched unrelated* SCT, received *graft vs host disease* prophylaxis with tacrolimus and low dose methotrexate	- Persistent hyponatremia - Significant eosinophilia (8 weeks after SCT) - Serum strongiloides IgG negative - Biopsy from endoscope: duodenal mucosa with s tercoralis - Stool examination: ova and parasites present - Serum strongyloides IgG (-) - Serum osmolarity check□ SIADH	EGD: mild diffuse inflammation in the gastric corpus and duodenum	- S. stercoralis hyperinfection - SIADH	- Empirical with albendazole 400 mg orally 2x/day for 3 days - Prenisone 20 mg pO 2x/day and budesonide - Definitive: Ivermectin 200 mg/kg orally per day until 3 days of negative stool for 2 weeks.	Normal sodium after 1 week and eosinophilia improved after 1 week of ivermectin therapy
Melexopoulou et al. 2017[15]	Female, 72 years old	Right-sided chest pain and discomfort in the right shoulder for 10 days, mild non-productive cough	- Travel history denied - CKD on HD for 9 years, renal transplant 2 years ago□ immunosuppressants mycophenolate sodium, tacrolimus, methylprednisolone (TAC (serum level, 8.8 ng/mL), MNa (360 mg 2x/day), and MP (4 mg/day)) CMV prophylaxis with valganciclovir for 3 months, and cotrimoxazole pneumocystis pneumonia for 4 months.	- Hemoglobin, 11.3 g/dL; - leukocytes, 14.2 K/mL; neutrophils, 89%; lymphocytes, 5%; - platelet, 235 K/mL; - ESR, 30 mm/h; - CRP, 125 mg/L; - Serum sodium, 124 mEq/L; - Serum creatinine, 0.6 mg/d - bronchoalveolar lavage material: branching Gram-positive rods surrounded by PMN cells, and gram staining and modified ZiehlNeelsen	- Persistent hyponatremia - CXR: normal - CT thorax: bilateral nodular lesions without mediastinal lymphadenopathy - CT head: dbn - CT shoulder: 2 large muscle abscesses	- SIADH - Systemic nocardiosis	- Persistent hyponatremia - Fluid restriction - Immunosuppressant agent adjustment□ TAC dose reduction to serum levels of 5 ng/mL - Systemic cotrimoxazole 15 mg/kg/day and imipenem 1.5 g/day for 2 weeks followed by oral cotrimoxazole for a total of 12 months - Abscess drainage	2 months pain has reduced cough is still felt, after 6 months it becomes, asymptomatic, 9 months = normal

				BTA showed branching organisms. - Abscess culture: Nocardia spp. - Thyroid and adrenals = normal - Plasma and urine osmolality SIADH				
Tariq et al. 2017[16]	Male, 37 years old	Abdominal pain for 2 weeks (periumbilical, radiating (-), 4/10, intermittent, no triggering factor), nausea, poor appetite, persistent vomiting, chronic diarrhea, 50 pounds weight loss over 6 months, frontal headache (sometimes with dizziness for several weeks), aggravated by vomiting and diffuse abdominal pain during treatment. TTV normal, kakeksia, oral mucosa dry, eye discharge dehydration, mild periumbilical pain, BU hypoactive	- Hypoosmolar hyponatremia (improving) - Hypertension, - Hypertension of both parents - Drink 3-4 beers per week	- Mild anemia, - Hypochloride, - Neutrophil-dominant leukocytosis, - Thrombocytophilia - Persistent hyponatremia - Low TSH, normal t3, normal ft4 subclinical hyperthyroidism - Cortisol stiumulation test normal - Urine: low serum somolarity, low urine osmolality, low urine sodium - EGD biopsy: extensive strongiloidosis with lymphocytic and focal eosinophilic infiltrates - Serology human t cell lymphotrophic virus (HTLV) 1 and 2 positive - HIV and Rapid plasma reagent (-)	- CT scan of the head and neck no cause of SIADH - CT scan abdomen: *partial small bowel obstruction* without masses - EGD: edema, white spot intestinal impression duodenal lymphangiectasia	- Persistent hyponatremia ec SIADH - Strongiloidiasis hyperinfection syndrome and disseminated extensive gastrointestinal involvement - Human T cell lymphotropic virus infection	- Hypertonic saline followed by normal saline - Water restriction - Diet restrictive medium chain triglyceride MCT (low fat, high protein diet) - Antiemetics - Antibiotics: metronidazole and ciprofloxacin - Ivermectin from day 18 - NGT decompression	Duration of treatment was 29 days, diarrhea and vomiting improved within 2 days. Symptom resolution was complete and hyponatremia i

Saradna et al. 2018[17]	Female, 67 years old	Lack of appetite for the past 10 days, fatigue for the past 3 months, dysphagia or burning sensation in the throat during swallowing, abdominal pain, GI bleeding. Tachycardia, tachypnea, frailty, wasting, dry mucous membrane, bilateral lower lung field *crackles*, mild diffuse abdominal tenderness	- Hispanic patients who were born in Mexico and migrated to the United States at the age of 37 years old - Breast cancer in 2002 had undergone surgery but refused chemotherapy - Vit B12 deficiency, - Peptic ulcer, - Left hip atroplasty aged 64 years, - Similar complaints and was admitted to another hospital for endoscopy with findings of prepyloric peptic ulcer and anemia.	- Hyponatremia - BTA sputum serial negative - MTB culture positive - PT and *partial thromboplastin time* elongated - Mild elevation of alkaline phosphatase - Normal thyroid and cortisol - Stool: strolingoides - Respiratory biopsy: granuloma - Bronchoscopic lavage: BTA negative but strongiloides positive - Gastrointestinal specimen (from Strongyloides stercoralis positive endoscopy.	- Evidence of MTB infection in lung, liver and KGBs - Autopsy miliary tuberculosis - CXR: 7 mm nodule in right lower lung field - Echo: LVEF 60-65% - Computed tomography (CT) of the thorax: >100 pulmonary nodules suggestive of miliary tuberculosis, - Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) - Endoscopy: multiple gastric ulcers with clots in duodenal diverticulum accompanied by embolization of bleeding vessels	- Strongiloides hyperinfection - Miliary tuberculosis - SIADH - Septic shock (day 5) - Candida esophagitis	- Fluid restriction 1 L/day followed by half normal saline and half sodium bicarbonate - Ivermectin 9 mg/24 hours + fluconazole - Prophylactic antibiotics for gram-negative bacteremia: piperacillin and tazobactam - ICU: vasopressors, broad-spectrum antibiotics, mechanical ventilation	Died on day 15 from septic shock with DIC

The initial search yielded 330 studies. A total of nine duplicate studies, as well as 110 narrative reviews or non-English studies, were excluded. A total of 211 studies were screened for relevance of title and abstract. Only 27 studies passed the title and abstract screening, and full text reviews were conducted. Based on the full text review, only 10 studies were included in the final analysis, 5 studies were excluded due to lack of access to the full text, and 12 studies were excluded for not listing systemic infection as a cause. The case studies are summarized in Table 1, and the baseline patient characteristics are listed in Table 2.

Table 2. Characteristics of refractory hyponatremia patients with systemic infection

Variabel	Result
Age (mean [SD])	49.63 (20.79)
Gender	
Man	7 (63.64%)
Woman	4 (36.36%)
Systemic Infection	
Hiperinfection *Strongyloides stercoralis*	5 (54%)
Tuberculosis	1 (9%)
Nocardiosis systemik	1 (9%)
Infection VZV diseminata	3 (28%)
Immunocompromised	
Tuberculosis milier	2 (18%)
HTLV infection	1 (9%)
Imunosupresan	
Resipien transplantation ren	1 (9%)
Resipien SCT	3 (28%)
Lepra	1 (9%)
ITP	1 (9%)
NHL	1 (9%)
HIV infection	1 (9%)
Pathophysiology Hyponatremia	
SIADH	10 (91%)
CSWS	1(9%)

Notes: VZV: *Varicella Zoster Virus*, HTLV: *Human T-Lymphotropic Virus*, SCT: *Stem Cell Transplantation*, ITP: *Immune Thrombocytopenic Purpura*, NHL: *Non-Hodgkin Lymphoma*, HIV: *Human Immunodeficiency Virus*, SIADH: *Syndrome of Inappropriate Anti Diuretic Hormone*, CSWS: *Cerebral Salt Wasting Syndrome*.

DISCUSSION

Patient Characteristics

A total of 11 patients were analyzed. The mean age of the patients was 46.63 years, with most of them being male (63.64%). Strongyloides stercoralis hyperinfection was the most common systemic infection in patients (54%). It was followed by disseminated varicella-zoster virus (VRZ) infection (28%), tuberculosis (9%), and cytemic nocardiosis (9%). The conditions that triggered patients' immune systems to weaken were mostly immunosuppressant treatment recipients (73%), such as those who had a kidney transplant, a stem cell transplant (SCT), leprosy, immune thrombocytopenic purpura (ITP), or non-Hodgkin lymphoma (NHL). Miliary tuberculosis was the second most common predisposing factor at 18%, followed by Human Immunodeficiency Virus (HIV) and Human T-Lymphotropic Virus (HTLV) infections at 9% each. The pathophysiology of hyponatremia was predominantly SIADH (91%), with one case involving the CSWS mechanism (9%).

Hyponatremia in disseminated Varicella Zoster Infection

Most patients with disseminated VZV infection are immunocompromised due to HIV infection, chronic illness, or chemotherapy. SIADH is found in about two thirds of these cases of disseminated infection. It is thought to be caused by VZV-induced direct encephalitis of the posterior pituitary or chest wall.[9]

Disseminated infection inducing encephalitis could potentially explain two phenomena simultaneously, namely disseminated cutaneous involvement and SIADH in the first patient. However, many instances of disseminated encephalitis are challenging to diagnose clinically since viral culture in cerebrospinal fluid is not always possible. Instead, this patient's symptoms of encephalitis and hyponatremia may overlap. On the other hand, it is known that some regularly used drugs for HIV-infected patients (Pentamidine and Vidarabine) can trigger SIADH.

However, a drug-induced cause of SIADH in this patient could be ruled out, as none of these drugs were given to the patient.[8] The second patient's central nervous system involvement in disseminated VZV infection was confirmed by cerebrospinal fluid (CSS) analysis, but there was no imaging or cellular evidence of inflammation in the brain or pituitary gland. Therefore, the local mechanism causing the release of anti-diuretic hormone remains uncertain. The third patient had some similarities with the second patient, but due to limited examination results, the cause of hyponatremia and its association with disseminated VZV infection are still unclear.[9] In the fiftth patient, disseminated VZV infection was caused by low CD4 levels, in addition to a history of chemotherapy and radiation in NHL. Hyponatremia due to SIADH was proposed as a frequent manifestation after conventional chemotherapy for NHL patients, but the

influence of disseminated infection on SIADH was not further elucidated.[11]

Hyponatremia in Tuberculous Meningitis with Sepsis

The fourth patient presented with hyponatremia that was refractory to fluid correction and was later found to have a background of cerebral salt wasting syndrome (CSWS). Hyponatremia due to CSWS, unlike the other cases, is a differential diagnosis of SIADH.[10] CSWS is a condition characterized by hyponatremia with elevated urinary sodium levels and hypovolemia that has a very different treatment compared to SIADH. Patients with SIADH are subjected to fluid restriction, while those with CSWS require fluid administration and sodium supplementation.[18]

The mechanism of CSWS, as well as hyponatremia in this condition, is still a matter of debate. The first mechanism is related to the release of natriuretic peptides in the form of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP).[10] ANP is released due to increased atrial strain and increased ventricular load from a surge in sympathetic outflow.[19] BNP is thought to be released by brain tissue in response to brain injury and enters the systemic circulation through a compromised blood-brain barrier.[18] ANP and BNP may also be released by the hypothalamus as a protective mechanism against increased intracranial pressure. These two natriuretic peptides are hypothesized to inhibit sympathetic outflow, the renin-aldosterone system, and vasoconstrictor peptide production, ultimately resulting in decreased aldosterone efficacy and a reduction in the kidney's ability to reabsorb sodium.[19] BNP, more specifically, acts on the renal ductus collectivus to inhibit sodium reabsorption and decrease renin release.[18] The second mechanism, the injured sympathetic nervous system, is thought to no longer be able to promote sodium reabsorption and is therefore unable to re-stimulate renin release due to hypothalamic injury.[18] Furthermore, CSWS may be a direct injury to the renal sympathetic innervation. This is shown by the fact that the disruption of sympathetic nerve input to the juxtaglomerular apparatus can make it harder for kidneys to reabsorb sodium, urate, and water in the renal proximal tubules, as well as decrease the release of renin and aldosterone.[20]

Hyponatremia in S. stercoralis hyperinfection

Strongyloides stercoralis hyperinfection occurs when filariform larvae spread to various organs, causing end-organ damage.[17] Most patients with hyperinfection have a history of living in or visiting areas endemic for S. stercoralis, and there are conditions that lead to an immunosuppressed status in patients. In immunocompromised patients, the host defense system is dysregulated, resulting in the loss of normal innate and adaptive defenses against helminth infection. In addition, hematogenous spread of worms also allows enteric bacteria to enter the bloodstream through damaged mucosa. As a result, mortality is very high (up to 87%) due to secondary bacteremia/sepsis or meningitis from these enteric pathogens.[16]

The sixth patient had a history of migration from Colombia, South America, a region endemic for S. stercoralis infection, as well as travel to Venezuela. The patient was also on oral corticosteroid therapy for ITP, which predisposes to disseminated infection with this species. However, the patient did not have any central nervous system manifestations or pulmonary infiltration; therefore, the mechanism by which this hyperinfection induced SIADH remains unclear.[12]

Another patient, 37, had a history of migration from Mexico, an endemic area for S. stercoralis, with no subsequent travel history. This raised the likelihood of chronic infection while living in the United States. This patient also had disseminated tuberculosis infection, which increases the predisposition to Strongyloides hyperinfection. On the other hand, Strongyloides hyperinfection can trigger the reactivation of latent tuberculosis. A decreased lymphocyte count also increases the risk. The patient's SIADH caused hyponatremia that was resistant to fluid restriction; miliary pulmonary tuberculosis was suspected of causing SIADH in this patient.[17]

However, persistent hyponatremia can occur due to prolonged vomiting symptoms, or vice versa, due to sodium dilution in cases of fluid retention. One possible mechanism is SIADH, which occurs when plasma osmolality is low, potassium levels are normal, and there is no significant pulmonary and central nervous system pathology.[13,14] In cases of persistent hyponatremia and terminal hypoglycemia, the presence of SIADH indicates adrenal insufficiency in sepsis or disseminated abdominal malignancy.

In the seventh pasient, there was an adrenal crisis after adrenal hemorrhage, the trigger of which was unknown and was most likely caused by sepsis or strongyloides hyperinfection. Protein-losing enteropathy caused by seere-manutrition can cause mmunodeficiency, but in this patient, the corticosteroids that were given for ITP (at least 20 mg/day) were the most important factor.[13] The tenth patient's immunodeficiency condition was a result of a history of alcohol abuse and HTLV-1 infection.[16]

Hyponatremia in Nocardiosis Systemic

The ninth patient was at risk of nocardia infection

due to long-term therapy for graft rejection and thir advanced age. Systemic nocardiosis causes inappropriate release of antidiuretic hormone (ADH), which leads to hypotonic hyponatremia and impaired water excretion. SIADH frequently occurs in hospitalized patients, and its causes can be classified as malignancy, pulmonary, or central nervous system disorders, including medication. In this patient, SIADH is likely due to eutopic ADH production related to the patient's pulmonary nocardiosis, as central nervous system involvement can be ruled out through head CT scans. This syndrome can also be associated with the use of tacrolimus, but in this patient, the treatment was unlikely to affect SIADH, as the patient improved with anti-microbials and fluid restriction, even though tacrolimus was routinely administered.[15]

CONCLUSION

Hyponatremia refractory can be seen in patients with systemic infection who have undergone therapy, which may be mediated by SIADH, CSWS, or other mechanisms. Most systemic infections are underpinned by one or more conditions that weaken the immune system. Several therapies for systemic infections lead to hyponatremia refractory. Treatment for the condition can vary depending on the therapy mechanism; for example, fluid restriction can improve SIADH, while replacement fluid administration is necessary for CSWS. In addition, addressing the primary issue of systemic infection should remain the top priority in treating the patient, irrespective of any potential side effects. On the other hand, treatment of systemic infection is still prioritized due to its contribution to the patient's hyponatremia state.

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Conflict of Interest
The authors have no conflicts of interest

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Author Contributions
This study has been carried out simultaneously by DRI and supervised BP, R, and J

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