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Severe Hyponatremia with Normokalemia in Pembrolizumab-Lenvatinib Combination Therapy for Metastatic Renal Cell Carcinoma: A Case of Suspected Secondary Adrenal Insufficiency and Clinical Differentials

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ABSTRACT

The combination of Pembrolizumab and Lenvatinib has become the standard first-line treatment for advanced renal cell carcinoma (RCC). However, the overlapping toxicity profiles of immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) create significant diagnostic challenges, particularly regarding electrolyte disturbances. Differentiating ICI-induced secondary adrenal insufficiency from TKI-induced toxicity or syndrome of inappropriate antidiuretic hormone (SIADH) is critical, especially in resource-limited settings where rapid hormonal assays are unavailable. A 67-year-old male with metastatic clear cell RCC presented with confusion, fatigue, and nausea 14 days after initiating palliative Pembrolizumab and Lenvatinib. He had a history of partial nephrectomy and was on Candesartan. Evaluation revealed severe hypotonic hyponatremia (113 mmol/L), acute kidney injury (Creatinine 2.2 mg/dL), and a hypertensive crisis (BP 229/138 mmHg). Notably, despite renal impairment and angiotensin receptor blocker therapy, potassium levels were normal (4.2 mmol/L). The hyponatremia was refractory to 3% hypertonic saline. Suspecting secondary adrenal insufficiency, empiric high-dose corticosteroids were administered, resulting in rapid normalization of serum sodium and resolution of symptoms. In conclusion, in patients receiving ICI-TKI therapy, the specific profile of severe hyponatremia with normokalemia—particularly in the context of renal insufficiency and RAAS blockade—serves as a high-value clinical indicator of preserved mineralocorticoid function. This points toward secondary adrenal insufficiency rather than primary adrenal injury or TKI-induced renal tubular acidosis. This case underscores the utility of deductive physiology in oncology practice.

1. Introduction

The management of advanced renal cell carcinoma (RCC) has undergone a dramatic transformation over the past decade, transitioning from an era of limited efficacy to one of targeted precision and immunomodulation.[1] Historically, RCC was considered a radio-resistant and chemo-resistant malignancy, with treatment options limited to cytokine therapies such as high-dose Interleukin-2 and Interferon-alpha, which offered modest efficacy but significant toxicity.[2] The elucidation of the Von Hippel-Lindau (VHL) pathway and the subsequent development of targeted therapies against vascular endothelial growth factor (VEGF) marked the first major paradigm shift. More recently, the advent of immunotherapy, specifically immune checkpoint inhibitors (ICIs), has further redefined the standard of care.[3]

Currently, the combination of Pembrolizumab, a potent monoclonal antibody targeting the programmed cell death protein-1 (PD-1), and Lenvatinib, a multi-targeted tyrosine kinase inhibitor (TKI) of VEGFR receptors, represents a cornerstone in the first-line treatment of advanced RCC.[4] The pivotal CLEAR trial demonstrated that this combination significantly improved progression-free survival (PFS) and overall survival (OS) compared to sunitinib alone.[5] However, the synergistic efficacy of this regimen is accompanied by a complex and often overlapping toxicity profile. Lenvatinib is well-known to cause adverse events such as hypertension, fatigue, proteinuria, and gastrointestinal disturbances. Concurrently, Pembrolizumab is associated with a unique spectrum of side effects termed immune-related adverse events (irAEs), which can affect any organ system but have a predilection for the endocrine glands. While thyroid dysfunction is the most common endocrine irAE, adrenal insufficiency (AI) is a rare but potentially fatal complication.[6]

The diagnostic challenge for the internist arises when a patient presents with non-specific symptoms such as fatigue, nausea, and electrolyte disturbances.[7] Both Lenvatinib toxicity and adrenal insufficiency can manifest with these symptoms. In major academic centers, the differentiation is facilitated by rapid access to pituitary magnetic resonance imaging (MRI) and hormonal assays, including serum cortisol, adrenocorticotropic hormone (ACTH), and cosyntropin stimulation tests.[8] However, in many healthcare settings globally, these diagnostic modalities are either unavailable or subject to significant turnaround delays. In such resource-limited contexts, the clinician must rely on clinical heuristics and readily available biochemical markers to make time-sensitive therapeutic decisions.[9]

This study is novel in its specific isolation and physiological deconstruction of hyponatremia with normokalemia as a definitive pathophysiological marker that distinguishes ICI-induced central (secondary) adrenal insufficiency from TKI-induced renal toxicity or primary adrenal injury.[10] The primary aim of this study is to establish this electrolyte pattern as a reliable sentinel sign to guide emergency management. We aim to demonstrate that the preservation of potassium levels in the setting of severe, refractory hyponatremia effectively rules out primary mineralocorticoid deficiency and strongly supports a diagnosis of isolated cortisol deficiency, justifying immediate empiric corticosteroid replacement in patients where confirmatory hormonal testing is delayed or unavailable.

2. Case Presentation

The patient is a 67-year-old male of Southeast Asian descent who presented to the Emergency Department of Wangaya Regional General Hospital, a tertiary referral center in Denpasar, Bali. To fully appreciate the complexity of his acute presentation, one must first examine the trajectory of his oncological history, which established the physiological vulnerabilities that would define his hospital course. Approximately 18 months prior to the current admission, the patient was diagnosed with a localized renal malignancy. Histopathological evaluation following surgery confirmed a clear cell renal cell carcinoma (ccRCC), the most common histological subtype of renal cancer, originating from the proximal convoluted tubule epithelial cells. At the time of the initial diagnosis, the tumor was classified as ISUP (International Society of Urological Pathology) Grade 1, indicating a low-grade neoplasm with a relatively favorable prognosis. The surgical management involved a partial nephrectomy of the affected kidney. While this nephron-sparing approach is the gold standard for preserving renal function, it inevitably left the patient with a reduced functional renal mass—effectively a solitary functional kidney status with limited reserve capacity. This anatomical history is paramount, as it rendered the patient uniquely susceptible to hemodynamic shifts and nephrotoxic insults.

Following the surgery, the patient entered a period of surveillance. However, recent follow-up imaging shattered the hope for a surgical cure. Computed tomography (CT) scans of the chest revealed the development of multiple new pulmonary nodules consistent with metastatic dissemination. The emergence of these distant metastases fundamentally altered the goals of care from curative to palliative (life-prolonging). In accordance with the current National Comprehensive Cancer Network (NCCN) guidelines and the practice-changing results of the phase 3 CLEAR trial, the oncological team initiated a first-line metastatic systemic therapy regimen. The chosen regimen was the double-hit combination of Pembrolizumab, a humanized monoclonal antibody targeting the programmed cell death protein-1 (PD-1) receptor on lymphocytes, and Lenvatinib, a multi-targeted tyrosine kinase inhibitor (TKI) acting on vascular endothelial growth factor receptors (VEGFR1-3), Fibroblast growth factor receptors (FGFR1-4), and other pathways involved in tumor angiogenesis and proliferation. Recognizing the patient's advanced age of 67 and his compromised renal reserve due to the prior partial nephrectomy, the treating oncologists opted for a risk-adapted dosing strategy. Lenvatinib was initiated at a reduced dose of 10 mg orally once daily, rather than the standard 20 mg starting dose used in the CLEAR trial, to mitigate the risk of severe nephrotoxicity and hypertension. Pembrolizumab was administered at the standard dose of 200 mg intravenously, scheduled every three weeks.

The patient's background medical history further complicated the clinical picture. He suffered from essential hypertension and chronic atrial fibrillation, both of which required rigorous pharmacological management. His home medication regimen, which he adhered to with high fidelity, included Candesartan 4 mg once daily, an angiotensin receptor blocker (ARB) chosen for its renal-protective properties; Rivaroxaban 7.5 mg twice daily, a direct oral anticoagulant (DOAC) for stroke prevention in non-valvular atrial fibrillation; and Bisoprolol 1.25 mg once daily, a cardioselective beta-blocker for rate control. This medication profile, specifically the use of an ARB in a patient with a solitary kidney, set the stage for a unique physiological conflict when the acute pathology eventually struck. Detailed demographic and clinical history data are presented in Table 1.

The clinical deterioration began with remarkable rapidity. The onset of symptoms occurred merely 14 days following the initiation of the Pembrolizumab and Lenvatinib regimen. This timeline is of significant clinical interest. While TKI-mediated toxicities such as hypertension and fatigue are known to occur within the first cycle, immune-related adverse events (irAEs) like hypophysitis typically have a median onset of 3 to 6 months. A presentation at two weeks represents a hyper-acute toxicity profile, possibly suggesting a heightened immunological sensitivity or the unmasking of a subclinical pre-existing endocrine deficit by the physiological stress of the new therapy. For the first week of therapy, the patient remained asymptomatic. However, on day 8, he began to complain of a vague, persistent epigastric discomfort. This pain was non-radiating and was initially attributed by the patient to indigestion or gastritis, a common side effect of oral TKIs. Over the subsequent days, this discomfort evolved into a profound, crushing fatigue (asthenia) that confined him to bed. The family noted that he became increasingly withdrawn, refusing food due to persistent nausea, though he denied any episodes of emesis.

The prodrome culminated in a frightening neurological decline over the 48 hours preceding hospital admission. The patient's wife reported that he became progressively confused, asking repetitive questions and struggling to find words (anomic aphasia). He became disoriented to time, believing it was the wrong year, and eventually grew lethargic, sleeping for 18 to 20 hours a day. This alteration in sensorium prompted the family to bypass their primary care provider and bring him directly to the Emergency Department at Wangaya Regional General Hospital. Upon arrival at the Emergency Department, the patient presented a diagnostic dilemma of immediate high acuity. Triage nurses noted a patient who was lethargic, pale, and clearly systemically unwell. The initial vital signs revealed a critical hemodynamic conflict: a hypertensive emergency. The non-invasive blood pressure measurement returned a reading of 229/138 mmHg.

Table 1. Patient Demographics, Medical History, and Medication Profile

CLINICAL CATEGORY & DETAIL	
DEMOGRAPHICS & COMORBIDITIES	
Age / Gender	67 Years / Male
Comorbidities	Hypertension Atrial Fibrillation
ONCOLOGICAL HISTORY	
Diagnosis	Clear Cell Renal Cell Carcinoma (ccRCC) ISUP Grade 1
Surgical History	Partial Nephrectomy Performed 18 months prior
Current Status	Pulmonary Metastases First-line Metastatic Setting
ACUTE PRESENTATION	
Chief Complaint	Generalized Fatigue, Epigastric Pain, Nausea Duration: 7 days
Neurological Status	Impaired Verbal Coherence Confusion reported by family
ACTIVE THERAPY & MEDICATIONS	
Immunotherapy / TKI	**Initiated 14 days prior to symptoms** **Pembrolizumab** (ICI) 200 mg IV q3 weeks **Lenvatinib** (TKI) 10 mg PO daily
Concomitant Meds	Candesartan 4 mg OD Rivaroxaban 7.5 mg BID Bisoprolol 1.25 mg OD

Abbreviations: ccRCC: clear cell Renal Cell Carcinoma; ICI: Immune Checkpoint Inhibitor; TKI: Tyrosine Kinase Inhibitor; IV: Intravenous; PO: Per Os (Oral); OD: Once Daily; BID: Twice Daily.

This extreme elevation in arterial pressure places the patient at imminent risk of end-organ damage, including hemorrhagic stroke, aortic dissection, or acute pulmonary edema. In the context of his medication history, this was immediately recognized as a likely consequence of Lenvatinib toxicity. Lenvatinib, by inhibiting VEGF signaling, halts the production of nitric oxide in the vascular endothelium, leading to potent and diffuse vasoconstriction. This vascular stiffness was superimposed on his baseline essential hypertension, overwhelming his low-dose Bisoprolol and Candesartan regimen.

Simultaneously, the patient's heart rate was 88 beats per minute and irregular, confirming the persistence of his atrial fibrillation despite the metabolic stress. He was afebrile (36.7°C), and his respiratory rate was 20 breaths per minute with an oxygen saturation of 98% on room air, suggesting that despite the extreme afterload caused by the hypertension, his left ventricle had not yet failed into frank pulmonary edema. The initial neurological assessment revealed a Glasgow Coma Scale (GCS) of 14 (E4, V4, M6). While he opened his eyes spontaneously and obeyed motor commands, his verbal response was confused. He was oriented to his own identity but disoriented to place and time. The neurological examination did not reveal any focal deficits—there was no hemiparesis, facial droop, or asymmetric reflex pathology—which argued against a large-territory ischemic stroke or intracerebral hemorrhage, despite the severe hypertension. This focused the differential diagnosis on metabolic encephalopathy rather than a structural neurological catastrophe, detailed in Figure 1.

Figure 1. Admission vital signs and hemodynamic profile.

A rigorous physical examination was conducted to ascertain the patient's volume status, a critical step in the differential diagnosis of the anticipated electrolyte disturbances. The physical exam of the hyponatremic patient is notoriously difficult, but specific signs were sought to categorize him as hypovolemic (dehydrated), euvolemic, or hypervolemic (fluid overloaded). The patient appeared older than his stated age, with evident temporal wasting suggestive of the catabolic state of metastatic malignancy. He was lethargic, requiring tactile stimulation to maintain engagement during the exam. The mucous membranes of the oral cavity were notably moist, and there was pooling of saliva under the tongue. The ocular globes were firm, not sunken. There was no scleral icterus or conjunctival pallor. These findings strongly argued against significant dehydration (hypovolemia), which would typically present with dry mucous membranes and sunken eyes. The jugular venous pressure (JVP) was not elevated, visible at approximately 2 cm above the sternal angle at 45 degrees. Precordial palpation revealed a non-displaced apical impulse. Auscultation confirmed an irregular rhythm consistent with atrial fibrillation, but crucially, there were no S3 or S4 gallops to suggest acute heart failure decompensation. Lung fields were clear to auscultation bilaterally. There were no crackles (rales) or wheezes. This absence of pulmonary congestion in the setting of a blood pressure of 229/138 mmHg was a testament to the patient's preserved left ventricular ejection fraction, suggesting that the hypertension was a primary vascular constriction issue rather than a volume-overload state. The abdomen was soft and non-distended. There was tenderness to deep palpation in the epigastrium, correlating with his chief complaint, but there was no guarding, rebound tenderness, or rigidity to suggest a surgical emergency like a perforated viscus (a known risk of both TKIs and steroids). Bowel sounds were present and normoactive. Skin turgor was preserved; when pinched over the clavicle, the skin snapped back immediately. There was absolutely no peripheral edema (pedal or sacral). This lack of edema is the hallmark of euvolemia. If the patient had heart failure or cirrhosis causing hyponatremia, edema would be expected. If he were dehydrated from Lenvatinib-induced diarrhea, turgor would be reduced. The patient was clinically Euvolemic. This categorization narrowed the differential diagnosis of his confusion and potential electrolyte issues to a select few conditions: Syndrome of inappropriate antidiuretic hormone (SIADH), glucocorticoid deficiency (Secondary Adrenal Insufficiency), or severe Hypothyroidism.

The results of the initial laboratory panel arrived, presenting the clinical team with a profound physiological paradox that would become the central intellectual challenge of the case. The complete blood count (CBC) revealed a hemoglobin of 14.9 g/dL, which was normal, arguing against acute hemorrhage or severe anemia of chronic disease. The white blood cell (WBC) count was elevated at 13.100/μL (Reference: 4000–10.000/μL). A detailed review of the differential showed a neutrophilic predominance. While leukocytosis can indicate infection, in this oncological context, it is often a paraneoplastic phenomenon or a marker of physiological stress (demargination of neutrophils). Platelets were mildly low at 106.000/μL, likely a side effect of the TKI therapy or mild hypersplenism. The renal profile was alarming. The serum creatinine had risen to 2.2 mg/dL, a sharp increase from his baseline of 1.1 mg/dL. In a patient with a solitary functional kidney (post-partial nephrectomy), this represented a critical loss of glomerular filtration rate (GFR)—an acute kidney injury (AKI) stage 2 or 3. The blood urea nitrogen (BUN) was disproportionately elevated at 64 mg/dL, creating a high BUN: Creatinine ratio that could suggest a pre-renal component or a catabolic state. The most striking findings were in the electrolytes. The serum sodium was critically low at 113 mmol/L (Reference: 136–145). This represents severe, life-threatening hyponatremia, putting the patient at immediate risk of cerebral edema and seizures. The serum osmolality was confirmed to be low at 243 mOsm/kg, confirming true hypotonic hyponatremia. However, the true shock came from the potassium level. The serum potassium was 4.2 mmol/L (Reference: 3.5–5.5). This Normokalemia was physiologically incongruent with the rest of the clinical picture. Consider the forces acting on this patient's potassium. The patient has a solitary kidney that is failing (Cr 2.2). The kidney is the primary exit route for potassium. AKI usually causes hyperkalemia. The patient takes Candesartan daily. ARBs block the Angiotensin II receptor in the adrenal zona glomerulosa, directly inhibiting the secretion of aldosterone. Aldosterone is the hormone responsible for excreting potassium. TKIs can cause renal microvascular damage, further impairing tubular secretion. In a standard patient with a solitary kidney, AKI, and ARB therapy, Hyperkalemia is virtually guaranteed. If this patient also had Primary Adrenal Insufficiency (Addison's disease), which destroys the adrenal gland and halts aldosterone production completely, the potassium should have been dangerously high (likely >6.0 mmol/L). The fact that the potassium was perfectly normal (4.2 mmol/L) implied that a powerful force was actively excreting potassium to counteract the AKI and the ARB. That force could only be an intact, robustly functioning Zona Glomerulosa secreting high levels of aldosterone. This finding was the first clue that while the patient might have adrenal insufficiency, it was not primary (adrenal destruction) but secondary (pituitary failure), where the aldosterone pathway remains preserved, detailed in Figure 2.

Figure 2. The biochemical paradox: admission panel.

Before initiating aggressive therapy, it was imperative to rule out structural causes for the renal failure and abdominal pain. An urgent Abdominal Ultrasound was performed at the bedside. The scan visualized the remaining renal tissue. It demonstrated bilateral grade I hydronephrosis—a mild dilation of the renal pelvis that likely reflected the high urine flow rate or mild back-pressure, but was insufficient to explain the severe AKI (which usually requires high-grade obstruction). A simple cyst measuring 5.39 × 4.77 cm was noted in the right kidney, a benign finding unrelated to the acute presentation. Crucially, the corticomedullary differentiation was preserved. This sonographic sign indicates that the renal parenchyma is not scarred or fibrotic; the kidney is stunned (acute injury) rather than dead (chronic disease). This provided hope that the renal function could recover if the underlying cause was treated. The liver scan was negative for metastatic nodules, ruling out acute hepatic failure as a cause of the metabolic derangement. Pleural ultrasound revealed minimal bilateral effusions, likely a capillary leak phenomenon often seen with TKIs or mild volume redistribution. Brain imaging (CT/MRI) was not immediately available to rule out pituitary metastasis or central nervous system causes of SIADH. This limitation meant the team had to rely on the biochemical profile and response to treatment to localize the pathology to the pituitary gland, detailed in Figure 3.

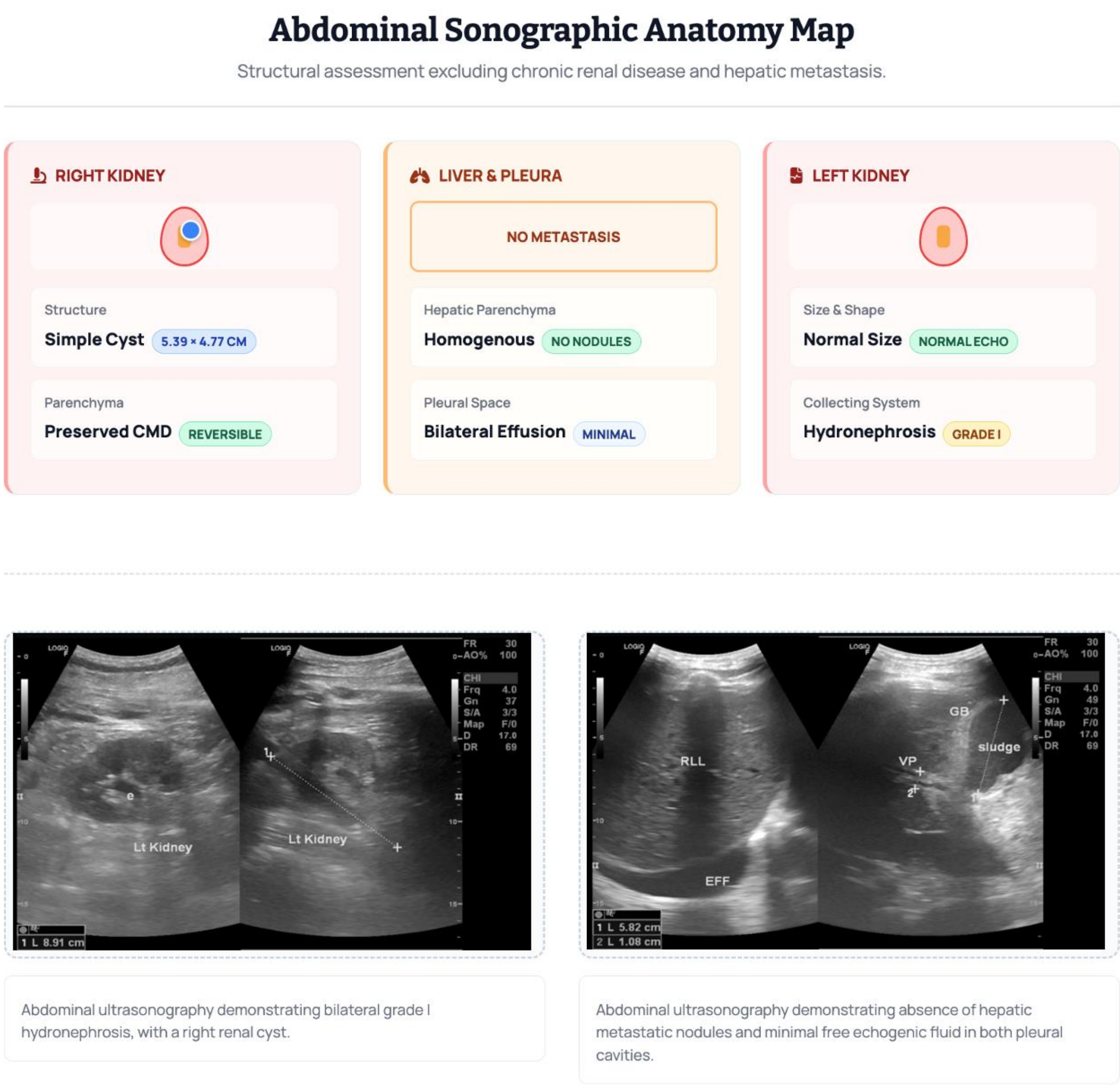

Figure 3. Abdominal sonographic anatomy map.

The patient was admitted to the High Care Unit (HCU), a step-down setting allowing for continuous cardiac telemetry and frequent neurological checks. The immediate management plan required navigating a treacherous path between two opposing emergencies: the Hypertensive Crisis (which required vasodilation) and the Severe Hyponatremia (which ostensibly required sodium loading). The Initial Strategy (Day 0), the attending physicians initially postulated a diagnosis of Lenvatinib-associated toxicity or SIADH. Given the severity of the hyponatremia (113 mmol/L) and the neurological confusion, the standard of care is the administration of hypertonic saline to acutely raise the serum sodium and reduce cerebral edema. A central venous catheter was inserted, and an infusion of 3% Hypertonic Saline was initiated at a rate of 12 mL/hour. This is a potent osmotic agent. In a typical patient with hypovolemic hyponatremia or SIADH, such an infusion should trigger a steady rise in serum sodium. Simultaneously, the hypertensive crisis (229/138 mmHg) had to be managed. The team faced a safety dilemma: giving a volume load (saline) to a patient with extreme hypertension risks precipitating flash pulmonary edema or hemorrhagic stroke. To mitigate this, a continuous infusion of Nicardipine (a calcium channel blocker) was titrated to gently lower the Mean Arterial Pressure (MAP) by no more than 25% in the first 24 hours, ensuring renal perfusion was maintained to the solitary kidney. The Failure of Therapy (Day 1 - The Refractory Phase), by the morning of day 1, despite 16 hours of continuous 3% saline infusion, the follow-up laboratory results were disheartening. The serum sodium had dropped further to 111 mmol/L, then fluctuated to 113 mmol/L by the afternoon. This lack of response—Refractory Hyponatremia—was a pivotal diagnostic clue. If the patient had been volume depleted (Lenvatinib diarrhea), the saline should have corrected the sodium rapidly. If it were simple SIADH, there would usually be some response to hypertonicity. The complete stagnation suggested a powerful, unopposed driver of water retention. The patient was water-logged, not because he lacked salt, but because his kidney was physiologically locked in a water-retaining mode. The patient had Euvolemia, Refractory Hyponatremia, and Normokalemia. This triad is the classic signature of Glucocorticoid Deficiency. In the absence of cortisol, Antidiuretic Hormone (ADH) is disinhibited and secreted uncontrollably, regardless of osmolarity. This high ADH opens the aquaporin channels in the kidney, reclaiming all free water and diluting the serum sodium. No amount of salt can fix this aquaporin leak unless the ADH brake (cortisol) is restored.

By the evening of Day 1, the clinical team faced a critical decision. The patient was not improving. The differential diagnosis had narrowed to Pembrolizumab-induced Secondary Adrenal Insufficiency. The Gold Standard diagnostic step would be to measure serum Cortisol and ACTH. However, in this resource-limited setting, these assays are send-out tests taking 3-5 days to return—time this patient did not have. Relying on the Normokalemia Sentinel Sign—the deductive reasoning that the patient's preserved potassium ruled out primary adrenal failure and pointed to a pituitary etiology—the team decided to treat empirically. The risk of untreated adrenal crisis (circulatory collapse, death) outweighed the risks of steroid administration. The Intervention, at 20:00 on Day 1, the 3% saline was continued, but the patient was given a loading dose of Methylprednisolone 62.5 mg Intravenously. The Response (Day 2), the effect was nothing short of dramatic, confirming the diagnosis Ex Juvantibus (diagnosis by cure). 8 Hours Post-Steroid, serum sodium rose to 116 mmol/L. The water lock on the kidneys had been broken. The steroid had suppressed the ADH, closed the aquaporins, and allowed the patient to begin excreting free water (aquaresis). 16 Hours Post-Steroid, sodium rose to 119 mmol/L. The patient began to wake up. He recognized his wife and asked for water. 24 Hours Post-Steroid, sodium reached 122 mmol/L. The epigastric pain and nausea vanished. The creatinine also began to trend down, dropping from 2.2 mg/dL to 1.8 mg/dL. This confirmed that the AKI was not purely structural (TKI toxicity) but had a significant hemodynamic component: cortisol is required to maintain glomerular arteriolar tone. Replacing the cortisol restored renal perfusion.

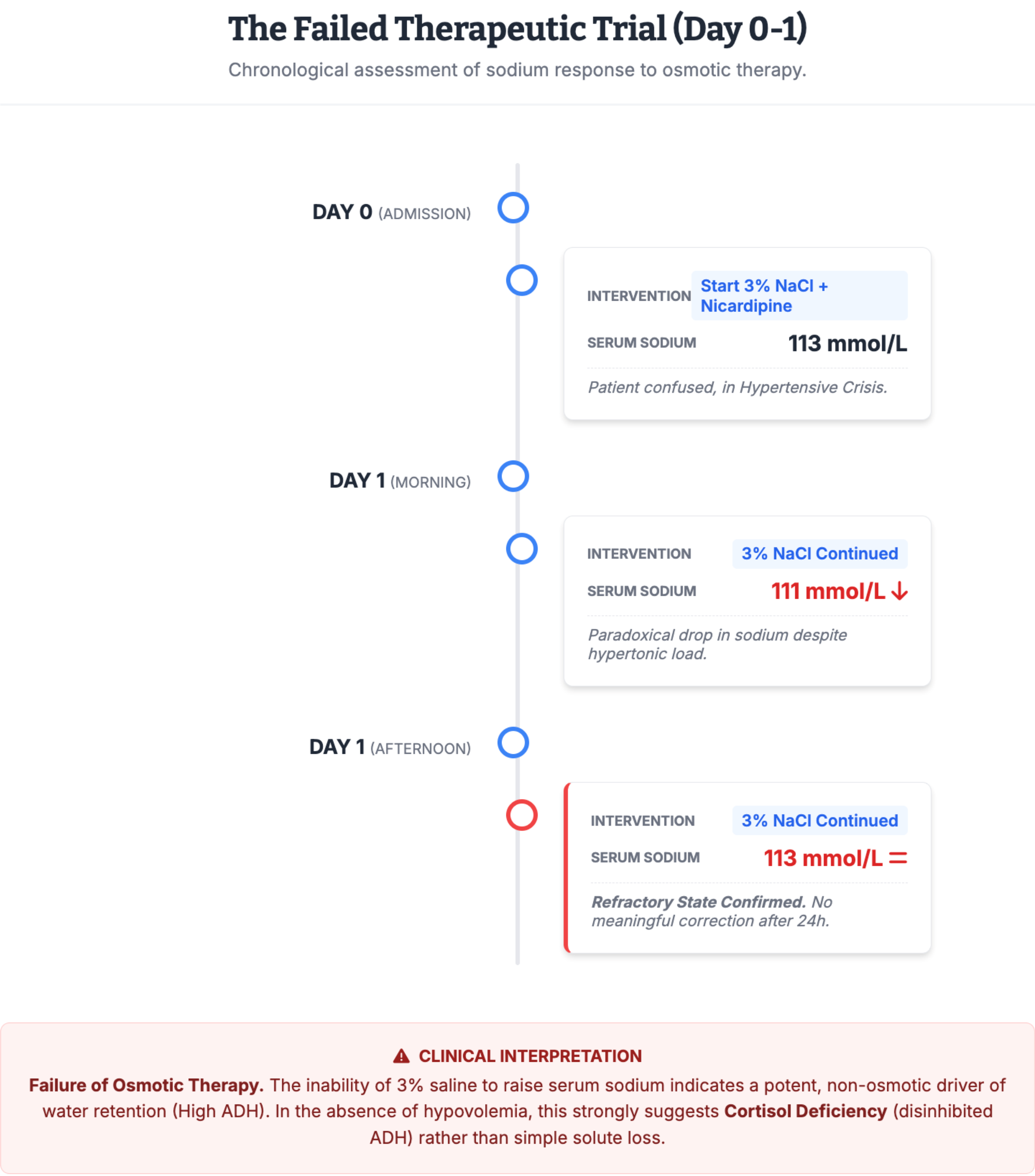

Figure 4. The failed therapeutic trial (Day 0-1).

By Day 3, the serum sodium had corrected to 127 mmol/L. The patient was fully oriented (GCS 15), ambulating with assistance, and tolerating a diet. The hypertensive crisis had resolved, likely due to the withdrawal of Lenvatinib and the normalization of his physiological stress response, allowing the Nicardipine drip to be weaned off. The intravenous Methylprednisolone was converted to oral Hydrocortisone, dosed at 10 mg in the morning and 5 mg in the afternoon to mimic the physiological circadian rhythm of cortisol secretion. On Day 4, with a serum sodium of 132 mmol/L and a creatinine of 1.4

mg/dL, the patient was deemed stable for discharge. He was counseled extensively on the sick day rules for adrenal insufficiency (doubling the steroid dose during fever or stress). The Lenvatinib and Pembrolizumab remained on hold pending a multidisciplinary oncology review to determine if and when immunotherapy could be safely rechallenged, potentially with lifelong steroid coverage, as detailed in Figure 5.

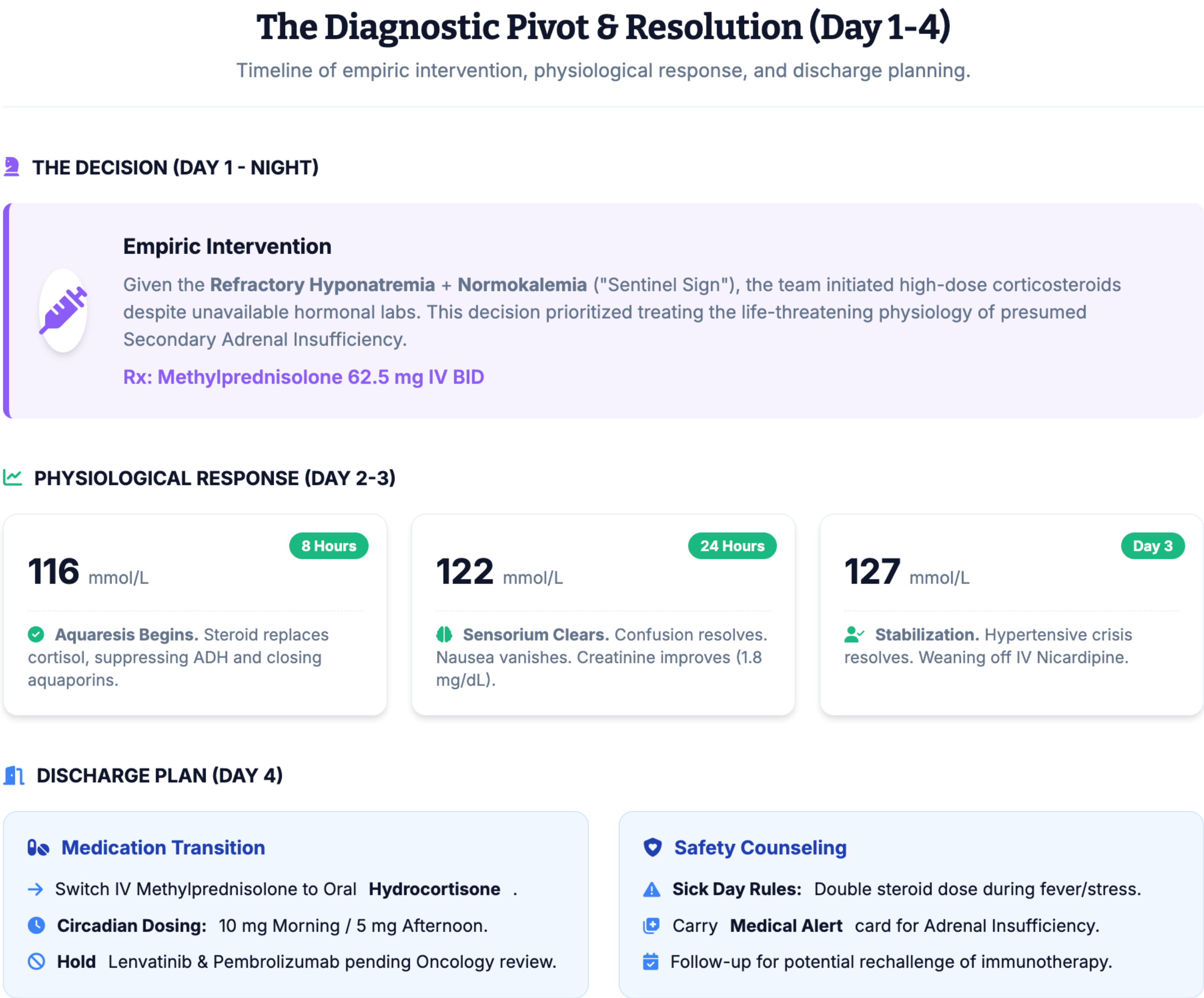

Figure 5. The diagnostic pivot and resolution (Day 1-4).

3. Discussion

The management of metastatic renal cell carcinoma has been fundamentally altered by the introduction of combination therapies that pair Immune Checkpoint Inhibitors with tyrosine kinase Inhibitors.[11] While the combination of Pembrolizumab and Lenvatinib offers robust oncological control, this case highlights the intricate and often perilous diagnostic landscape that clinicians must navigate when these agents induce overlapping toxicities.[12] Figure 6 provides a schematic overview illustrating the critical pathophysiological distinction between Primary Adrenal Insufficiency

(Scenario A) and Secondary Adrenal Insufficiency (Scenario B) in the context of severe hyponatremia. Scenario A: Primary Adrenal Insufficiency (Addisonian Crisis) The left panel depicts the pathophysiology of Primary Adrenal Insufficiency, a condition characterized by the direct destruction of the adrenal cortex (e.g., due to autoimmune adrenalitis or hemorrhage). In this scenario, the pituitary gland remains intact and appropriately attempts to stimulate the adrenal glands. However, the destruction of the adrenal cortex results in a failure of all adrenocortical zones. Consequently, there is a deficiency in both Cortisol (from the zona fasciculata) and Aldosterone (from the zona glomerulosa). The loss of aldosterone, the body's primary mineralocorticoid, leads to uncontrolled renal sodium wasting and potassium retention. This manifests clinically as the classic Addisonian electrolyte profile: Hyponatremia (due to volume depletion and ADH release) coupled with Hyperkalemia. This profile is highlighted in red, indicating an impaired adrenal axis. Scenario B: Secondary Adrenal Insufficiency (The Patient's Phenotype) The right panel illustrates the pathophysiology of Secondary Adrenal Insufficiency, the condition suspected in this case (e.g., Pembrolizumab-induced hypophysitis). Here, the pathology originates centrally in the pituitary gland, leading to a failure of ACTH secretion. This results in a profound deficiency of Cortisol, as its production is ACTH-dependent. The lack of cortisol removes the negative feedback on Antidiuretic Hormone (ADH), leading to disinhibited ADH release, water retention, and dilutional Hyponatremia. Crucially, however, the adrenal cortex remains structurally intact but dissociated from pituitary control. The key physiological distinction lies in the preservation of the zona glomerulosa. Aldosterone secretion is primarily regulated by the Renin-Angiotensin-Aldosterone System (RAAS) and serum potassium levels, *not* by ACTH. Therefore, despite the pituitary failure, the adrenal gland retains the capacity to secrete Aldosterone. This preserved mineralocorticoid function allows the kidneys to continue excreting potassium normally. The bottom right panel synthesizes these mechanisms into the patient's observed phenotype: Severe hyponatremia (driven by cortisol deficiency and high ADH) coexisting with Normokalemia (maintained by intact aldosterone). This dissociation—termed the Sentinel Sign—serves as a powerful clinical indicator. In a patient with risk factors for hyperkalemia (such as Acute Kidney Injury and ARB therapy), the preservation of normokalemia effectively rules out primary adrenal destruction and strongly points to a central, pituitary etiology where mineralocorticoid function is spared. This matches the case findings and validates the diagnostic pivot to secondary adrenal insufficiency.[13]

The integration of Lenvatinib and Pembrolizumab creates a double-hit potential for adverse events. Lenvatinib, a potent inhibitor of VEGFR1-3, FGFR1-4, PDGFR-alpha, and RET, is well-documented to cause renal and vascular toxicity. The patient presented with a hypertensive crisis (blood pressure 229/138 mmHg), which is a classic hallmark of VEGF inhibition. Lenvatinib induces hypertension by inhibiting the VEGF-mediated production of nitric oxide in endothelial cells, leading to systemic vasoconstriction. This finding initially biased the clinical reasoning toward Lenvatinib toxicity. However, the severity of the hyponatremia (113 mmol/L) was disproportionate to what is typically observed with Lenvatinib alone. While TKIs can cause hyponatremia through gastrointestinal losses or rare instances of SIADH-like syndromes, the patient’s euvolemic status and lack of significant diarrhea argued against volume depletion as the primary driver. Conversely, Pembrolizumab targets the PD-1 receptor to unleash T-cell cytotoxicity against tumors but can simultaneously trigger autoimmune destruction of endocrine tissues. The challenge in this case was the black box scenario created by the unavailability of hormonal assays. Without serum cortisol or ACTH levels, the clinician is forced to rely on deductive physiology.[14]

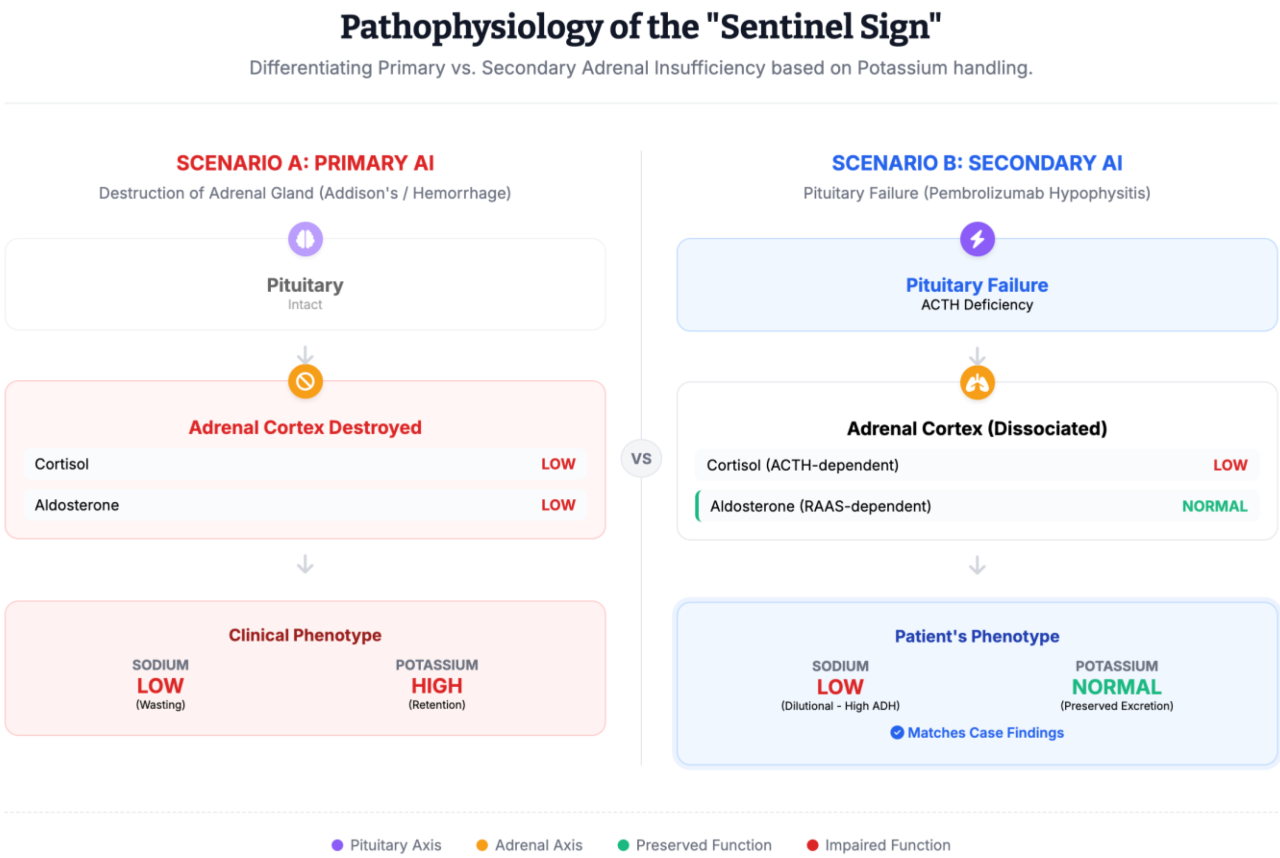

Figure 6. Pathophysiology of the sentinel sign.

To understand the diagnostic weight of the serum sodium level, one must appreciate the non-osmotic regulation of antidiuretic hormone (ADH), also known as Arginine Vasopressin. Under normal physiological conditions, cortisol exerts a crucial negative feedback effect on the secretion of corticotropin-releasing hormone (CRH) and ADH from the hypothalamus and posterior pituitary. Cortisol acts as a physiological brake on ADH release. In the setting of secondary adrenal insufficiency, such as Pembrolizumab-induced hypophysitis, the pituitary fails to secrete ACTH, leading to atrophy of the adrenal zona fasciculata and a precipitous drop in cortisol. The absence of cortisol removes the inhibitory brake on ADH. Consequently, ADH levels rise inappropriately relative to serum osmolality.[15] This elevated ADH binds to V2 receptors on the basolateral membrane of the renal collecting duct principal cells, triggering a cAMP-dependent cascade that inserts Aquaporin-2 channels into the apical membrane. The result is avid free water retention and dilutional hyponatremia. This mechanism explains why the patient's hyponatremia was refractory to 3% hypertonic saline. The pathology was not a solute deficit but a failure of water excretion driven by unchecked ADH. The administration of salt without replacing the missing cortisol failed to address the underlying aquaporin leak. Only the administration of methylprednisolone, which mimics the physiological action of cortisol, restored the negative feedback loop, suppressed ADH, and allowed for the excretion of excess free water.[16]

The most pivotal finding in this study is the preservation of normokalemia (4.2 mmol/L) in a patient with multiple risk factors for hyperkalemia. The patient had severe acute kidney injury (Creatinine 2.2 mg/dL) superimposed on a solitary kidney, and he was taking Candesartan, an angiotensin receptor blocker (ARB). In a typical clinical scenario, the combination of a solitary kidney, AKI, and RAAS blockade would inevitably lead to hyperkalemia due to impaired distal potassium secretion. The fact that this patient maintained a normal potassium level is physiologically extraordinary and serves as the key to localizing the endocrine lesion.[17]

In primary adrenal insufficiency (Addison's disease), the entire adrenal cortex is destroyed, affecting the zona glomerulosa (aldosterone), zona fasciculata (cortisol), and zona reticularis (androgens). The loss of aldosterone leads to renal sodium wasting and potassium retention. If this patient had suffered from primary adrenalitis or Lenvatinib-induced adrenal hemorrhage, the lack of aldosterone combined with the AKI and ARB would have resulted in life-threatening hyperkalemia. However, in Secondary Adrenal Insufficiency, the pathology is central (pituitary). While ACTH is lost, leading to cortisol deficiency, the zona glomerulosa is preserved because aldosterone secretion is primarily regulated by the renin-angiotensin-aldosterone system (RAAS) and serum potassium levels, not by ACTH. Therefore, despite the pituitary failure, the patient's adrenal gland retained the capacity to secrete aldosterone.[18] This intact aldosterone drive was robust enough to excrete potassium against the gradients imposed by the AKI and the candesartan. This specific electrolyte dissociation—severe hyponatremia with normokalemia—effectively ruled out primary adrenal injury and strongly pointed to a central etiology, allowing the team to diagnose secondary AI with high confidence.

It is imperative to rigorously exclude Lenvatinib as the primary cause of the renal and electrolyte derangement. Lenvatinib can induce renal injury via thrombotic microangiopathy (TMA) or podocyte injury, leading to proteinuria. In cases of severe Lenvatinib-induced renal failure, particularly in a patient with a solitary kidney, one would expect oliguria and impaired potassium excretion leading to hyperkalemia. The absence of hyperkalemia in our patient is inconsistent with pure Lenvatinib-induced acute tubular necrosis or TMA. Furthermore, the rapid improvement in renal function (creatinine decreasing to 1.4 mg/dL) following steroid administration suggests that the AKI had a significant hemodynamic component related to cortisol deficiency (which maintains renal perfusion pressure) rather than irreversible structural damage from the TKI. While the hypertension was clearly TKI-mediated, the metabolic picture was dominated by the ICI-mediated endocrinopathy.

The decision to treat empirically with high-dose corticosteroids in a patient with a hypertensive crisis is complex and requires careful consideration of safety.[19] Administering 3% hypertonic saline, a volume expander, to a patient with a blood pressure of 229/138 mmHg carries a significant risk of precipitating acute decompensated heart failure (flash pulmonary edema) or posterior reversible encephalopathy syndrome (PRES). In this case, the refractory nature of the hyponatremia to saline necessitated a change in strategy. While corticosteroids can acutely worsen hypertension via mineralocorticoid receptor cross-reactivity, treating the underlying adrenal insufficiency is often necessary to stabilize hemodynamics. The rapid resolution of the patient's confusion and electrolyte abnormalities validates the risk taken. However, in resource-limited settings where infectious diseases such as tuberculosis or Strongyloides stercoralis are endemic, the use of high-dose steroids without screening carries the risk of reactivation or hyperinfection syndrome. Clinicians must weigh these risks carefully. The Exjuvantibus diagnosis—diagnosis confirmed by response to treatment—validated the hypothesis in this case, but it should be reserved for scenarios where the clinical suspicion is high, and the risk of delay outweighs the risk of empiric treatment.

A notable feature of this case is the onset of symptoms just 14 days after the initiation of immunotherapy. Immune-related hypophysitis typically presents with a median onset of 3 to 6 months. An onset at two weeks is an outlier and raises several possibilities. It may represent a hyper-acute immune reaction, possibly exacerbated by the inflammatory milieu created by the concurrent TKI therapy and the presence of metastatic disease. Alternatively, the patient may have had subclinical pre-existing pituitary dysfunction that was unmasked by the physiological stress of the hypertensive crisis and the TKI initiation. This rapid timeline underscores the importance of maintaining a high index of suspicion for irAEs even in the very early cycles of treatment, contradicting the traditional teaching that these events are exclusively delayed phenomena.[20]

This comprehensive review of a single case illuminates a critical diagnostic pathway for the modern oncologist and internist. We conclude that in patients treated with the Pembrolizumab-Lenvatinib combination, the development of severe hyponatremia with preserved potassium levels acts as a high-fidelity sentinel sign for Secondary Adrenal Insufficiency. This electrolyte profile allows for the rapid differentiation of ICI-induced central endocrinopathy from TKI-induced renal toxicity or primary adrenal injury. The physiological basis lies in the specific loss of ACTH-driven cortisol (causing hyponatremic water retention via ADH) with the concurrent preservation of the Renin-Angiotensin-Aldosterone system (maintaining potassium homeostasis). For clinicians practicing in resource-limited environments, identifying this Hyponatremia with Normokalemia pattern provides a scientific justification to initiate life-saving empiric corticosteroid therapy, potentially averting the catastrophic consequences of missed adrenal crisis.

4. Conclusion

The intersection of targeted therapy and immunotherapy has revolutionized cancer care but introduced a new spectrum of diagnostic challenges. This case report validates the utility of hyponatremia with normokalemia as a specific clinical marker for Pembrolizumab-induced secondary adrenal insufficiency in patients also receiving Lenvatinib. By distinguishing this central endocrinopathy from primary adrenal damage and TKI toxicity, clinicians can expedite appropriate treatment with corticosteroids, even in the absence of advanced hormonal diagnostics. This approach highlights the enduring value of detailed physiological reasoning in the management of complex oncological emergencies.

5. References

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