CASE REPORT

Acute Psychosis Secondary to Isolated Adrenocorticotropic Hormone Deficiency Treated with Imatinib

Masaru Nakamura[1)], Takahiko Nagamine[2)]

ABSTRACT

Objective: **Isolated adrenocorticotropic hormone (ACTH) deficiency is a pituitary disorder which causes secondary adrenal insufficiency. ACTH secretory cell damage resulting from hypophysis has been implicated in the etiology of this disorder.**

Design: **Isolated ACTH deficiency primarily presents with physical symptoms of adrenal insufficiency, however, sometimes shows various psychotic symptoms.**

Materials and Methods: **A 61-year-old-man with schizophrenia who had received imatinib as postoperative adjuvant therapy for gastrointestinal stromal tumor presented to our department because of gradual cognitive dysfunction.**

Results: **The temporal correlation between the eosinophilia after imatinib treatment and the appearance of euvolemic hyponatremia with low serum ACTH and cortisol levels supported that the previous imatinib treatment contributed to isolated ACTH deficiency. His psychiatric symptoms and life-threating physical conditions including adrenal crisis improved with antipsychotic and glucocorticoid hormone replacement therapy.**

Discussions: **We hypothesized that previous imatinib treatment inhibited Programmed Cell Death Protein 1 (PD-1)/ Programmed Cell Death Ligand 1 (PD-L1) expressed on activated T cells and cancer cells, which induced hypophysitis leading to the development of isolated ACTH deficiency.**

Conclusions: **Psychiatric symptoms rather than physical symptoms can be highlighted in isolated ACTH deficiency because of deficiency in glucocorticoids. Therefore, clinician should consider such physical disease when treating patients with psychotic symptoms.**

KEY WORDS

adrenocorticotropic hormone deficiency, hypophysitis, imatinib, psychosis, secondary adrenal insufficiency

INTRODUCTION

Acute psychosis may be caused by psychiatric disorders, but also from medical conditions or psychoactive drugs. Endocrine diseases can affect psychotic symptoms because of hormone imbalance. Isolated adrenocorticotropic hormone (ACTH) deficiency causes secondary adrenal insufficiency because of impaired secretion of ACTH, but not of the other hormones of anterior pituitary gland. ACTH secretory cell damage resulting from hypophysis and autoimmune mechanisms due to tumors, systemic diseases, infection or drug-induced causes have been implicated in the etiology of this disorder[1)]. ACTH deficiency primarily presents with physical symptoms such as weight loss, skin dryness and low blood pressure of adrenal insufficiency, however, when psychological symptoms such as malaise, apathy and depression are prominent, their conditions can be mistakenly diagnosed as a psychotic disorder[2)]. Blood chemistry frequently show mild anemia, eosinophilia, hypoglycemia, hypotension and hyponatremia because affected patients are deficient in glucocorticoids. Definite diagnosis simply requires low or no serum ACTH and cortisol levels under corticotrophin-releasing hormone (CRH) challenge test. Whereas, early diagnosis is not always easy, since the isolated ACTH deficiency gradually and latently develops with non-specific symptoms.

Tyrosine kinase inhibitors (TKIs) including imatinib and immune checkpoint inhibitors (ICIs) have been reported to contribute to hyponatremia via various mechanisms such as syndrome of inappropriate antidiuretic hormone secretion (SIADH) and immune-related adverse events (irAEs)[3)]. Immunotherapy with immune ICI monoclonal antibodies, which has shown to be a therapeutic effective alternative in several malignant tumors, may be accompanied by autoimmune endocrine adverse effects such as thyroiditis and hypophysitis. Isolated ACTH deficiency has also been recently reported to be associated with ICI monoclonal antibodies[4)].

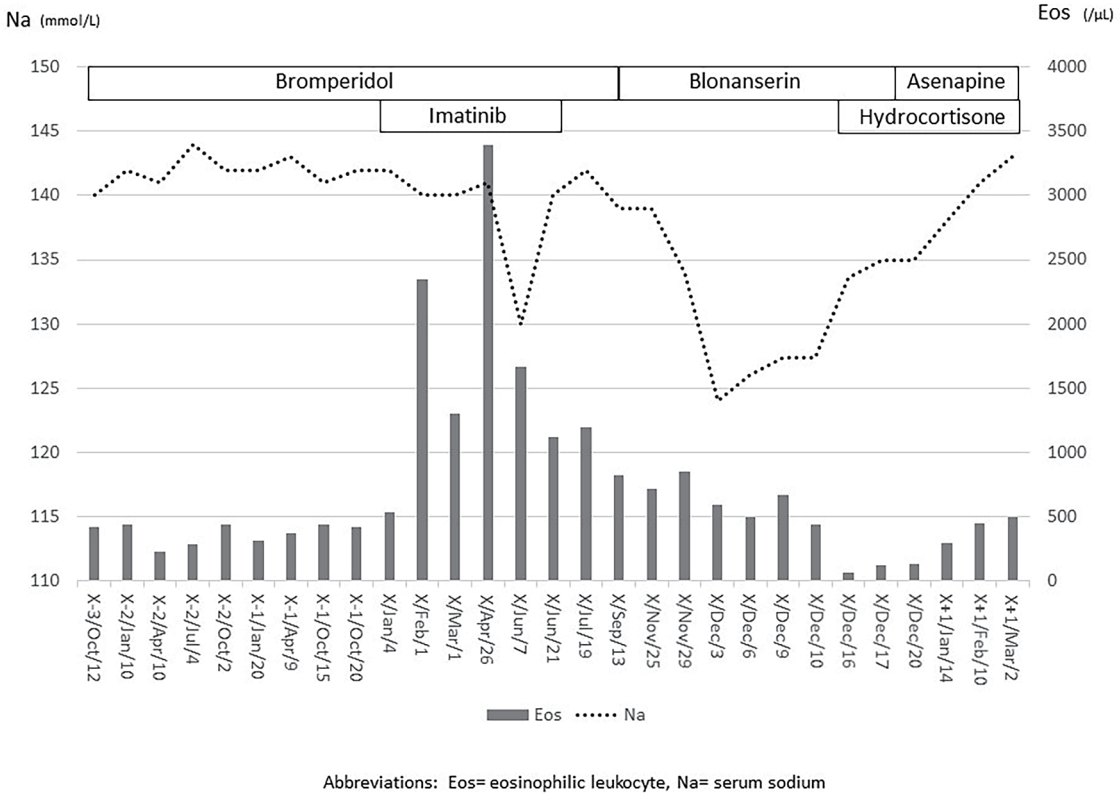
Here, we presented a case of initial onset of isolated ACTH deficiency in a male patient with schizophrenia, which was most likely caused by previous imatinib treatment and appeared with eosinophilia and euvolemic hyponatremia during the hospitalization. His acute psychotic symptoms mimicking an exacerbation of schizophrenia and life-threating physical conditions finally improved with antipsychotic and glucocorticoid hormone replacement therapy.

CASE PRESENTATION

A 61-year-old man with a 37-year history of schizophrenia was presented to our psychiatric hospital due to a slowing down of thought and a strange behavior such as wandering thereabout at day and night. He

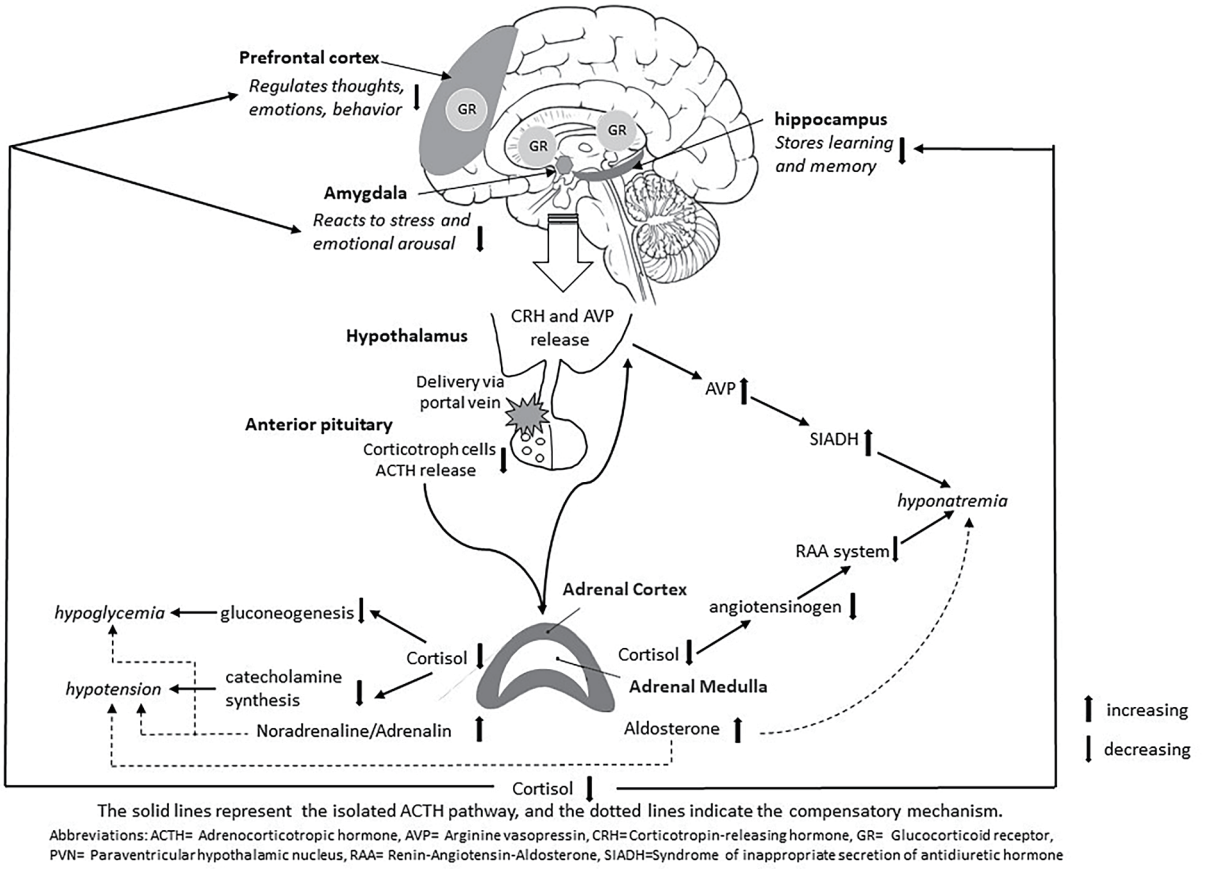
Received on July 23, 2023 and accepted on August 4, 2023
1) Kosekai-Kusatsu Hospital
Hiroshima, Japan
2) Sunlight Brain Research Center
Yamaguchi, Japan
Correspondence to: Takahiko Nagamine
(e-mail: tnagamine@outlook.com)

ORCID ID:
Masaru Nakamura: 0000-0002-8894-9792
Takahiko Nagamine: 0000-0002-0690-6271



Abbreviations: Eos= eosinophilic leukocyte, Na= serum sodium

Figure 1: Clinical course of antipsychotics, imatinib and hydrocortisone treatment and changes in eosinophilic leukocyte counts and serum sodium concentrations



The solid lines represent the isolated ACTH pathway, and the dotted lines indicate the compensatory mechanism.

Abbreviations: ACTH= Adrenocorticotropic hormone, AVP= Arginine vasopressin, CRH= Corticotropin-releasing hormone, GR= Glucocorticoid receptor, PVN= Paraventricular hypothalamic nucleus, RAA= Renin-Angiotensin-Aldosterone, SIADH=Syndrome of inappropriate secretion of antidiuretic hormone

Figure 2: Schematic representation of the hypothalamic-pituitary-adrenal axis and its link to the central glucocorticoid receptors in isolated adrenocorticotropic hormone deficiency

had been treated with bromperidol, biperiden, cloxazolam, arotinolol hydrochloride, and furosemide in the clinics of psychiatry and internal medicine. He underwent laparoscopic subtotal gastrectomy for gastrointestinal stromal tumor (GIST) of stomach at the age of 59. He had received postoperative adjuvant imatinib mesilate 400 mg/day for 7 months, which resulted in discontinuation 4 months ago because of anasarca without findings of local recurrence and distant metastasis in the postoperative follow-up duration. At the time of admission, his mental status examination represented delusion of reference with decreased motivation and reduced spontaneous speech. His vital signs, physical examination, chest X-ray, whole body computed tomography scanning and 12-lead electrocardiogram were unremarkable except dry skin and low blood pressure of 78/46 mmHg. Laboratory work-up showed low red blood cell counts of 3.92 million/μL (reference, 4.35-5.55 million/μL), low hemoglobin concentration of 11.6 g/dl (13.7-16.8 g/dL), high eosinophils percentage of 14% (0%-6.0%) with normal white blood cell counts, low serum albumin of 3.7 g/dL (4.1-5.1 g/dL), high creatinine phosphokinase (CK) of 794 IU/L (59-248 IU/L), high aspartate aminotransferase (AST) of 42 IU/L (13-30 IU/L), high lactate dehydrogenase (LDH) of 263 U/L (124-222 U/L), high serum creatinine (S-Cr) of 1.56 mg/dL (0.65-1.07 mg/dL), high blood urea nitrogen (BUN) of 28.2 mg/dL (8.0-20.0 mg/dL), high uric acid of 9.6 mg/dL (3.7-7.0 mg/dL), high N-terminal fragment pro-brain type natriuretic peptide (NT-proBNP) of 293pg/mL (< 125 pg/mL), high C-reactive protein (CRP) of 5.36 mg/dL (< 0.14 mg/dL), and low serum glucose of 51 mg/dL (73-109 mg/dL) with normal range of serum sodium, potassium, and chloride levels. His thyroid function showed high thyroid stimulating hormone of 9.065 mIU/ml (0.610-4.230 mIU/ml), low free thyroxine of 0.7 ng/dL (0.9-1.7 ng/dL) and normal free triiodothyronine of 2.6 pg/mL (2.1-4.1 pg/mL), while thyroglobulin antibodies and thyroid peroxidase antibodies tests were negative.

Blonanserin transdermal patch was used for his antipsychotic treatment because of subtotal gastrectomy and its minimal impact on metabolic disorders. There were no stereotypic movements and visual hallucinations, but the hypobulia and autistic symptoms did not resolve. After being given appropriate nutritional supplementary food with intravenous fluids, the patient's kidney function and the levels of serum CK, AST, LDH, CRP, and glucose returned to normal, but appeared low levels of serum sodium of 128, 124 mEq/L and chloride of 95, 92 mEq/L on day 6 and 9, respectively. Endocrine tests were carried out to investigate the cause of euvolemic hyponatremia on day 12, which revealed that he had considerable low levels of serum ACTH of < 1.5 pg/mL (7.2-63.3 pg/mL) and cortisol of < 0.5 μg/mL (4.5-21.1 μg/mL) suggesting secondary adrenal insufficiency.

For the further examination, he was transferred to the department of endocrinology and metabolism of the general hospital on day 15. The combined pituitary function test was performed to assess the anterior pituitary reserve for production of anterior pituitary hormones. Four exogenous hypothalamic releasing hormones; corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), luteinizing hormone-releasing hormone (LH-RH) and growth hormone-releasing peptide 2 (GHRP-2) were administrated and corresponding pituitary hormones were assessed every 15 or 30 minutes for the next two hours. Secretions of thyrotropin (TSH), luteinizing hormone (LH) follicle stimulating hormone (FSH) and growth hormone (GH) were maintained within normal limits, whereas those of ACTH and cortisol were diminished as presented in Tab. In addition, sufficient response of plasma cortisol concentration was confirmed in the rapid ACTH test (serum cortisol levels: < 0.00, 1.54, and 2.03 μg/dL, at baseline, after 15 and 30 minutes, respectively) Thus, he was diagnosed isolated ACTH deficiency. He was discharged on the eighth hospital day of the general hospital receiving oral hydrocortisone 15 mg/day and readmitted to our hospital to control his psychiatric symptoms and improve his undernutrition state.

However, on day 3 evening of the 2nd hospitalization to our hospital, a fever of 40.1℃ developed followed by deterioration of consciousness along with prolonged severe hypoxia, hypotension and hypoglycemia overnight. A chest computed tomography showed new patchy opacities in both lower lung lobes, and laboratory test showed leukocytosis with extreme high levels of serum procalcitonin of 49.43 ng/mL (< 0.05 ng/mL) on day 4, so, we considered that he was thrown into acute adrenal crisis with septicemia induced by severe aspiration pneumonia. He was transferred again to the emergency medical care center of the general hospital. Though, his consciousness disorder continued for several days despite systemic evaluation and treatment, he came to himself after drip infusion of 100 mg/day hydrocortisone, which was tapered off and switched to oral hydrocortisone 15 mg/day again. After he was moved from the emergency unit to the general ward of the hospital, he regained motivation for nutrition support therapy and rehabilitation, however, his speech with delusions worsened.

One month later, he experienced the 3rd time admission to our hospital to continue psychiatric and medical treatment and adapt himself to social life in the community. Since his psychiatric symptoms and serious physical conditions did not relapse and he recovered enough to talk about his future lifestyle, he was discharged from our hospital after next 3 months with concomitant use of asenapine and hydrocortisone.

Time sequential change of serum sodium levels and eosinophilic leukocyte counts in addition to the main therapeutic drugs which were associated with schizophrenia and isolated ACTH deficiency were presented in Figure 1. Afterwards, he has no recurrence of psychosis or any signs of adrenal insufficiency ten months after his last hospitalization.

DISCUSSION

The temporal correlation between eosinophilia after imatinib treatment and the appearance of euvolemic hyponatremia with low serum ACTH and cortisol levels supported that this TKI contributed to isolated ACTH deficiency, suggesting a hormonal disturbance due to immunotherapy-induced pituitary inflammation.

In this report, we highlighted the following three points: 1) imatinib induced hypophysitis leading to the development of isolated ACTH deficiency; 2) continuous monitoring of serum sodium levels and eosinophil counts contributed to the diagnosis of isolated ACTH deficiency; 3) psychiatric symptoms rather than physical symptoms can be highlighted in isolated ACTH deficiency.

Imatinib is the treatment of choice in patients with locally advanced or metastatic GIST, however, it carries adverse drug reaction (ADR). Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare but potentially life-threatening ADR in patients treated with imatinib[6]. In our patient, the severe organ damage such as DRESS syndrome were not observed while continuing imatinib treatment, however, his peripheral absolute eosinophil count increased up to 3,392 /μL and persisted more than 500 /μL despite withdrawal of imatinib treatment until he received glucocorticoid replacement therapy. So, there is a possibility that imatinib caused continuous eosinophilia which related to the development of ACTH deficiency in our patient. The prevalence of hyponatremia for imatinib in phase 2 clinical trials was 12.5%[5]. The most characterized mechanism of TKIs-related hyponatremia is SIADH[6,7]. Glucocorticoid deficiency, due to central/secondary adrenal insufficiency, is the key differential diagnosis for SIADH, because it presents with a similar euvolemic hyponatremia. The mechanisms for the development of hyponatremia in glucocorticoid deficiency are impaired renal water handling in the absence of circulating cortisol and increased plasma concentrations of arginine vasopressin (AVP), despite hypo-osmolality[8]. In our patient, the serum sodium levels transiently decreased to 130 mEq/L during imatinib treatment might be due to increased AVP levels in relation glucocorticoid deficiency, although neither plasma cortisol concentration nor AVP were measured before the hospitalization.

ICI have shown significant clinical benefits in tumor regression and survival for several malignancies. Anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-programmed death-1 (PD-1), which also has a ligand, PD-L1, act by activating the immune system and enhancing anti-tumor T-cell immunity[9]. However, the immune response generated by ICI can be complicated by several autoimmune adverse effects, including endocrinopathies[10]. ICI as well as TKIs have also been associated with electrolytes disturbances, the most frequent being hyponatremia[11,12]. Several case reports described ICI-induced hyponatremia due to hypophysitis and secondary adrenal insufficiency. In this setting, hypophysitis causes low ACTH levels and reduced cortisol secretion, and serum sodium is then decreased secondary to increased vasopressin levels resulting from reduced inhibition by cortisol[13]. The underlying mechanisms of ICI-related hypophysitis remain unverified, especially for PD-1/PD-L1 inhibitors. Kanie *et al*.[14] demonstrated 10% of PD-1/PD-L1 inhibitors-related hypophysitis were associated with the autoimmunity against corticotrophs and may be caused as a form of paraneoplastic syndrome, in which ectopic expression of ACTH in the tumor was observed. Seifert *et al*.[15] demonstrated that in human GIST cell lines, the combination of imatinib with PD-1/PD-L1 blockade enhanced the antitumor effects of imatinib by increasing T-cell effector function. Considering these findings, we hypothesized that imatinib treatment as adjuvant chemotherapy of GIST inhibited PD-1/PD-L1 expressed on activated T cells and cancer cells, which induced hypophysitis leading to the development of isolated ACTH deficiency.

We experienced a patient with GIST of stomach who developed iso-

lated ACTH deficiency with mild hypothyroidism during 7 months of imatinib treatment and exhibited isolated ACTH deficiency 4 months after the discontinuation. In other words, our case showed that hyponatremia and eosinophilia appeared earlier than secondary adrenal deficiency, implying potential association between them and the incidence of isolated ACTH deficiency. The previous reports indicated that the serum sodium level is regarded to be useful in predicting progression to isolated ACTH deficiency, and eosinophilia was also believed to be an early predictor of adrenal insufficiency in patients treated with anti-PD1 antibodies, respectively[16,17]. So, when patients have been treated with TKIs or ICIs, continuous monitoring of serum sodium levels and eosinophil counts may help early recognition of isolated ACTH deficiency.

Primary adrenal insufficiency is characterized by decreased aldosterone and cortisol production due to diminished adrenal gland function. Both primary adrenal insufficiency and secondary adrenal insufficiency represent symptoms of adrenal insufficiency, however, hyponatremia and hypotension are more common in primary adrenal insufficiency due to the volume depletion from the reduced mineralocorticoid function. Whereas, in secondary adrenal insufficiency, counter regulatory hormones (i.e., aldosterone and noradrenalin/adrenalin) can guard against low serum sodium level and low blood pressure.

The pathophysiology of psychosis in isolated ACTH deficiency is unclear. Narayan *et al*.[18] suggested that glucocorticoids decrement might increase conduction velocity along peripheral axons while prolonging conduction across synapses. If patients are receiving abnormally high sensory signals but are unable to integrate these signals appropriately, hallucinations and psychosis might develop. Holtzman *et al*.[19] has revealed pervasive effects of glucocorticoids on brain structure and function, including hippocampal abnormalities that have been linked with psychosis. Spiegel *et al*.[20] postulated that both hypercortisolemic and hypocortisolemic state result in psychosis. Throughout the limbic and paralimbic regions, (e.g., the hippocampus, amygdala, and prefrontal cortex), there are two types of receptors, mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs). Both animal and human studies indicated that the relative proportion of MRs to GRs activation might be an important moderating factor in multiple brain processes, with the relation of receptor activation to brain function such that too much or too little can impair cognitive processes. Psychiatric symptoms rather than physical symptoms can be highlighted in isolated ACTH deficiency, as shown in Figure 2.

CONCLUSION

We report a case of isolated ACTH deficiency with imatinib treatment similar to an exacerbation of schizophrenia. Based on the published researches, we speculated that imatinib treatment as adjuvant chemotherapy of GIST inhibited PD-1/PD-L1 expressed on activated T cells and cancer cells, which induced hypophysitis leading to the development of isolated ACTH deficiency. We believe this is the first published report of imatinib-induced secondary adrenal insufficiency in psychotic patients. Treatment of acute psychosis with antipsychotics need to be continued, and this patient had a good course with glucocorticoid hormone replacement therapy. Therefore, clinician should consider such physical disease when treating patients with acute psychosis.

REFERENCES

1. Langlois F, Varlamov EV, Fleseriu M. Response to Letter to the Editor from Asa and Mete: "Hypophysitis, the Growing Spectrum of a Rare Pituitary Disease". J Clin Endocrinol Metab. 2022; 107(5): e2208-e2209. https://doi.org/10.1210/clinem/dgac026.
2. Morigaki Y, Iga J, Kameoka N, Sumitani S, Ohmori T. Psychiatric symptoms in a patient with isolated adrenocorticotropin deficiency: case report and literature review. Gen Hosp Psychiatry. 2014; 36(4): 449.e3-5. https://doi.org/10.1016/j.genhosppsych.2014.02.012.
3. Pelletier K, Štrtić M, Kitchlu A. Cancer therapy-induced hyponatremia: A case-illustrated review. J Onco-Nephrology. 2021; 5(1): 70-78. https://doi.org/10.1177/23993693211002216.
4. Iglesias P, Sánchez JC, Díez JJ. Isolated ACTH deficiency induced by cancer immunotherapy: a systematic review. Pituitary. 2021; 24: 630-643. https://doi.org/10.1007/s11102-021-01141-8.
5. Kaur S, Singh S, Singh R, Singla P. DRESS syndrome induced by imatinib. J Postgrad Med. 2021; 67(3): 158-163. https://doi: 10.4103/jpgm.JPGM_746_20.
6. Hill J, Shields J, Passero V. Tyrosine kinase inhibitor-associated syndrome of inappropriate secretion of anti-diuretic hormone. J Oncol Pharm Pract. 2016; 22(5): 729-32. https://doi.org/10.1177/1078155215592023.
7. Liapis K, Apostolidis J, Charitaki E, Panitsas F, Harhalakis N, Nikiforakis E. Syndrome of inappropriate secretion of antidiuretic hormone associated with imatinib. Ann Pharmacother. 2008; 42(12): 1882-6. https://doi.org/10.1345/aph.1L410.
8. Garrahy A, Thompson CJ. Hyponatremia and Glucocorticoid Deficiency. Front Horm Res. 2019; 52: 80-92. https://doi.org/10.1159/000493239.
9. Melero I, Hervas-Stubbs S, Glennie M, Pardoll DM, Chen L. Immunostimulatory monoclonal antibodies for cancer therapy. Nat Rev Cancer. 2007; 7(2): 95-106. https://doi: 10.1038/nrc2051.
10. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med. 2018; 378(2): 158-168. https://doi.org/10.1056/NEJMra1703481.
11. Wanchoo R, Karam S, Uppal NN, Barta VS, Deray G, Devoe C, Launay-Vacher V, Jhaveri KD; Cancer and Kidney International Network Workgroup on Immune Checkpoint Inhibitors. Adverse Renal Effects of Immune Checkpoint Inhibitors: A Narrative Review. Am J Nephrol. 2017; 45(2): 160-169. https://doi.org/10.1159/000455014.
12. Seethapathy H, Rusibamayila N, Chute DF, Lee M, Strohbehn I, Zubiri L, Faje AT, Reynolds KL, Jhaveri KD, Sise ME. Hyponatremia and other electrolyte abnormalities in patients receiving immune checkpoint inhibitors. Nephrol Dial Transplant. 2021; 36(12): 2241-2247. https://doi.org/10.1093/ndt/gfaa272.
13. Joshi MN, Whitelaw BC, Palomar MT, Wu Y, Carroll PV. Immune checkpoint inhibitor-related hypophysitis and endocrine dysfunction: clinical review. Clin Endocrinol (Oxf). 2016; 85(3): 331-9. https://doi.org/10.1111/cen.13063.
14. Kanie K, Iguchi G, Bando H, Urai S, Shichi H, Fujita Y, Matsumoto R, Suda K, Yamamoto M, Fukuoka H, Ogawa W, Takahashi Y. Mechanistic insights into immune checkpoint inhibitor-related hypophysitis: a form of paraneoplastic syndrome. Cancer Immunol Immunother. 2021; 70(12): 3669-3677. https://doi.org/10.1007/s00262-021-02955-y.
15. Seifert AM, Zeng S, Zhang JQ, Kim TS, Cohen NA, Beckman MJ, Medina BD, Maltbaek JH, Loo JK, Crawley MH, Rossi F, Besmer P, Antonescu CR, DeMatteo RP. PD-1/PD-L1 Blockade Enhances T-cell Activity and Antitumor Efficacy of Imatinib in Gastrointestinal Stromal Tumors. Clin Cancer Res. 2017; 23(2): 454-465. https://doi.org/10.1158/1078-0432.CCR-16-1163.
16. Cho KY, Miyoshi H, Nakamura A, Kurita T, Atsumi T. Hyponatremia can be a powerful predictor of the development of isolated ACTH deficiency associated with nivolumab treatment. Endocr J. 2017; 64(2): 235-6. https://doi.org/10.1507/endocrj.EJ16-0596
17. Ariyasu R, Horiike A, Yoshizawa T, Dotsu Y, Koyama J, Saiki M, Sonoda T, Nishikawa S, Kitazono S, Yanagitani N, Nishio M. Adrenal Insufficiency Related to Anti-Programmed Death-1 Therapy. Anticancer Res. 2017; 37(8):4229-32. h t https://doi: 10.21873/anticanres.11814.
18. Narayan V, Narayanaswamy JC, Krishnakanth M, Muralidharan K. Atypical Neuropsychiatric Presentation of Addison's Disease: A Case Report. Prim Care Companion J Clin Psychiatry. 2008; 10(5): 412-3. https://doi: 10.4088/pcc.v10n0511b.
19. Holtzman CW, Trotman HD, Goulding SM, Ryan AT, Macdonald AN, Shapiro DI, Brasfield JL, Walker EF. Stress and neurodevelopmental processes in the emergence of psychosis. Neuroscience. 2013; 249: 172-91. https://doi.org/10.1016/j.neuroscience.2012.12.017.
20. Spiegel DR, Nelson AB, Lieb DC, Pattison AM, Smith J, Zigrossi P, Godbout E. A Case of Psychosis in a Patient with Secondary Adrenal Insufficiency: A Possible Etiological Role of a Hypocortisolemic-induced Increase in Proinflammatory Cytokines. Innov Clin Neurosci. 2017; 14(9-10): 4-10. eCollection 2017 Sep-Oct.