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CASE REPORT

Acute Adrenal Insufficiency Induced by Total Body Irradiation in a Recipient of an Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract: Radiotherapy used in the treatment of malignant disorders has been associated with the late emergence of chronic adrenal insufficiency. Reported here is an 18 years old male with acute lymphoblastic leukemia who received an allogeneic hematopoietic stem cell transplant following a conditioning therapy composed of total body irradiation and cyclophosphamide at King Faisal Specialist Hospital and Research Centre in Riyadh in October 2008. Four days following his allograft, the patient developed acute hypoadrenalism that responded well to corticosteroid replacement therapy. To our knowledge, this is the first case of radiation-induced acute adrenal insufficiency. In certain individuals who have specific risk factors for the development of hypoadrenalism, radiotherapy may precipitate Addisonian crisis which requires prompt diagnosis and urgent therapy.

Keywords: acute lymphoblastic leukemia, hematopoietic stem cell transplant, total body irradiation, graft versus host disease

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Introduction

Addison's disease (primary adrenal insufficiency) was first described by Thomas Addison in 1855.[1,2] It occurs in 1:100,000 population and has equal sex incidence.[2] There are three types of adrenal insufficiency: primary adrenal insufficiency, caused by destruction of adrenal cortex; secondary adrenal insufficiency, caused by deficient secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland and tertiary adrenal insufficiency, caused by deficient secretion of corticotrophin-releasing hormone (CRH) from the hypothalamus.[1]

The clinical manifestations of chronic primary adrenal insufficiency are non-specific and do not appear until at least 90% of the adrenal cortex has been destroyed, while acute adrenal insufficiency usually presents as refractory shock triggered by a physiologic stress or infection.[1] Despite being a rather rare endocrine disorder, Addison's disease is potentially fatal if not recognized early and treated promptly.[1,2]

Case Report

An 18 years old Saudi male with no known medical illnesses was transferred to King Faisal Specialist Hospital and Research Centre (KFSH&RC) from a local hospital in Riyadh on 08/04/27 for further evaluation of his pancytopenia. He presented to the local hospital with: (1) low back abscess treated with surgical drainage and broad spectrum antibiotics. (2) low blood counts; WBC: 3.02×10^9/L, Hb: 63 g/L, PLT: 34×10^9/L for which he received packed red blood cells and platelets. (3) fever, night sweats, anorexia and malaise for 2 weeks. Physical examination on admission to KFSH&RC revealed: a generally well young male with temperature of 36.7 °C, pulse rate of 96/minute, BP of 135/75 mm Hg and respiratory rate of 20/minute. There was pallor but no jaundice, leg edema or external palpable lymphadenopathy. Chest was clear and cardiovascular examination revealed an ejection systolic murmur over the left sternal edge with no added heart sounds. There was no abdominal tenderness and no palpable organomegaly. Neurological examination revealed no abnormality. Laboratory investigations showed: complete blood count (CBC): WBC: 2.8×10^9/L, Hb: 107 g/L, PLT: 90×10^9/L. Blood film revealed thrombocytopenia and circulating blast cells. Renal, hepatic and coagulation profiles were all within normal limits. Bone marrow examination [BME] was consistent with precursor-B acute lymphoblastic leukemia (ALL) with no cytogenetic abnormality. After confirming the diagnosis of ALL, the patient was commenced on 1423 ALL induction protocol that consisted of: prednisone, vincristine, cyclophosphamide, L-asparaginase and intrathecal methotrexate. On day 10 of chemotherapy, the patient developed septic shock due to *Klebsiella pneumoniae* bacteremia secondary to a perianal abscess which required intensive care unit admission for inotropic support for few days. The abscess was drained and cefepime and flagyl were replaced by meropenem. Day 14 BME showed evidence of residual leukemia with 11% blast cells. Meanwhile, the patient developed steroid-induced diabetes mellitus for which sliding scale of insulin was given. Taking into consideration the complications encountered and that more chemotherapy would be administered, it was decided not to start a new reinduction course of chemotherapy but to give the remaining part of the 1423 ALL induction protocol. Day 28 BME showed evidence of regeneration with no leukemia. During this course of treatment, 3 sessions of intrathecal methotrexate were given and cerebrospinal fluid was clear. On 08/06/04, the patient was sent home on: omeprazole 40 mg/day, fluconazole 200 mg/day and bactrim 960 mg twice daily. On 08/06/18, the patient was readmitted for a consolidation course of chemotherapy. He was asymptomatic and his examination revealed no new abnormality. Blood counts were normal and BME showed no leukemia. Thereafter, the patient received high dose cytosine arabinoside consolidation therapy without any complications. Meanwhile, an HLA-identical sibling donor was identified, so the patient was planned for an allogeneic hematopoietic stem cell transplant (HSCT). Prior to admission for HSCT, he was found to have relapse of his leukemia, so he was commenced on a salvage course of chemotherapy composed of fludarabine and cytosine arabinoside. During the neutropenic period following this therapy, the patient developed a pilonidal sinus that was surgically excised. Cultures from the surgical wound grew a multidrug resistant (MDR) *Pseudomonas aeruginosa* which was treated with intravenous (IV) colistin. Day 28 BME showed evidence of second complete remission (CR). After the recovery of his blood counts, the patient was sent

home on 08/09/28 on augmentin, ciprofloxacin and ranitidine. On 08/10/05, the patient was readmitted for HSCT. He was totally asymptomatic and his physical examination revealed no new abnormality. Laboratory investigations revealed normal blood counts, renal, hepatic and coagulation profiles. Pre-HSCT BME revealed evidence of second CR. Swabs taken from the site of the pilonidal sinus cultured MDR *Pseudomonas aeruginosa*, so IV colistin therapy was resumed and the HSCT was delayed by 2 weeks to allow wound healing and control of the local infection. Later on, the patient received a conditioning protocol composed of cyclophosphamide and fractionated total body irradiation (TBI) [12 Gy: 9 sessions over 3 days]. On 08/10/27, the patient received his allogeneic peripheral blood HSCT. The infused CD34 + cell count was 4.32×10^6/kg. The patient received graft versus host disease (GVHD) prophylaxis in the form of cyclosporine-A and methotrexate and infection prophylaxis in the form of bactrim, acyclovir and fluconazole. On day 4 HSCT, the patient developed profound fatigue and drowsiness. That time he had no fever, dyspnea, abdominal pain, bleeding etc. Physical examination revealed postural hypotension [blood pressure: 105/60 mm Hg dropping to 75/40 mm Hg on standing]. No mucocutaneous pigmentation or any other abnormality was found on repeated clinical evaluation and no new clinical focus of infection was detected. New septic screens and blood cultures were negative. Addison's disease was suspected and short synacthen test was arranged. Random serum cortisol was 41 nmol/L and results of the synacthen test were: baseline serum cortisol: 7 nml/L, serum cortisol 30 minutes after injection: 137 nmol/L and 60 minutes after injection: 206 nmol/L. Abdominal X ray and computerized axial tomography (CAT) scan of the adrenal glands did not show any evidence of calcification, mass lesions or bleeding in the adrenals. Plasma ACTH level was elevated and adrenal antibody screen was negative. After confirming the diagnosis of acute adrenal insufficiency, the patient was commenced on IV hydrocortisone 50 mg four times per day. One week later, the dose of hydrocortisone was reduced to 100 mg/day. He engrafted his leucocytes on day 15 and his platelets on day 17 HSCT. However, the patient developed the following complications in the early post-transplant period: (1) several febrile neutropenic and few septic episodes treated with various antimicrobials including: piperacillin-tazobactam, vancomycin, meropenem, amikacin, metronidazole and caspofungin. (2) grade III mucositis treated with total parenteral neutrition and IV morphine infusion. (3) bacteremia due to MDR *Pseudomonas aeruginosa* treated with IV colistin. (4) drug-related convulsions treated with phenytoin. (5) thrombotic thrombocytopenic purpura treated with replacement of cyclosporin-A by tacrolimus. (6) veno-occlusive disease of the liver treated with corticosteroids. (7) cytomegalovirus infection treated with foscarnet. (8) infection and drug related renal impairement treated with hydration, antimicrobials and withdrawal of the offending drugs. (9) acute GVHD of liver and gastrointestinal tract; grade III refractory to IV methylprednisolone, antithymocyte globulin, budesonide and cyclosporine-A treated with mycophenolate mofetil, tacrolimus and 12 sessions of extracorporal photophoresis. These complications lengthened his post-transplant hospitalization. Chimeric studies prior to discharge showed: myeloid cells: 96.4% donor and lymphoid cells: 92.4% donor. On 09/02/21 (Day 115 HSCT), the patient was clinically very well and his CBC showed: WBC: 2.65×10^9/L (neutrophils: 1.5), Hb: 106 g/L, PLT: 161×10^9/L. The renal and hepatic profiles were normal. The patient was sent home on the following medications: tacrolimus: 0.5 mg twice daily, mycophenolate mofetil: 500 mg twice daily, phenytoin 300 mg/day, penicillin 500 mg/day, fluconazole 200 mg/day, omeprazole 20 mg twice daily, vitamin D 400 units per day, calcium caltrate 600 mg/day, pentamidine 300 µg nebulizer once monthly, IV immunoglobulin 25 grams monthly and prednisone 30 mg alternating with 20 mg daily. Thereafter, the patient had regular follow up at the HSCT outpatient clinic.

Discussion

Autoimmune adrenalitis is the commonest cause of primary adrenal insufficiency in western countries. Tuberculosis is the commonest infectious cause worldwide and the commonest cause in the third world. Less common infectious causes include: syphilis, fungal and human immounodeficiency virus infections. Other causes of Addison's disease include: malignant disorders: lymphoma, melanoma and metastatic cancers of lung, breast, kidneys, bladder

and pancreas; anticoagulants; adrenal hemorrhage due to meningococeemia or warfarin; sarcoidosis; amyloidosis and adrenoleukodystrophy.[1–5]

The clinical features of Addison's disease include: anorexia, fatigue, muscle weakness, nausea, vomiting, diffuse abdominal pain, generalized pigmentation, hypotension which may be postural, thin and dark hair, nail melanonychia, lassitude, syncope, postural dizziness, diarrhea, constipation, myalgia, arthralgia, flexion contractures, amenorrhea, loss of libido and neuropsychiatric manifestations. The laboratory abnormalities in Addison's disease include: hyperkalemia, hyponatremia, hypercalcemia, hyperchloremia, azotemia, metabolic acidosis, anemia, lymphocytosis, eosinophilia, low serum aldosterone level, low plasma cortisol level, high renin and ACTH levels in addition to adrenal autoantibodies.[1,3] Electroencephalography may show diffuse slowing and bursts of sharp and slow wave discharges. Adrenal imaging by plain X-ray or computerized axial tomography (CAT) scan of the abdomen is usually required.[3]

Addisonian crisis may be precipitated by: severe surgical or accidental trauma, septic shock or serious infection e.g. meningococeemia or Pseudomonal bacteremia, bilateral adrenal hemorrhage or infarction e.g. due to anticoagulants, sudden withdrawal of prolonged steroid therapy and any new stress superimposed on chronic adrenal insufficiency.[1,3,6–8] The clinical features of this rare disorder incude: fever, nausea, vomiting, abdominal pain, dehydration, hypotension, weakness, shock, coma in addition to the other manifestations of Addison's disease.[1,3] Management of Addisonian crisis includes: immediate and prompt IV infusion of large volumes of isotonic saline solution, stress doses of steroids (hydrocortisone 100 mg IV Q 6 hourly) in addition to correction of electrolytic disturbances and treatment of the underlying cause. Once the condition is stable corticosteroid therapy can be tapered, then conversion to oral maintenance therapy and evaluation of the cause of the adrenal insufficiency should be perused. Mineralocorticoid therapy should be commenced prior to discontinuation of the saline solution infusion as mineralocorticoid deficiency is the major factor driving the course of adrenal crisis.[1]

The conventional replacement therapy in Addison's disease has been oral hydrocortisone 20–30 mg/day, equivalent to cortisone acetate 25–37.5 mg divided in 2 or 3 doses. Continuous subcutaneous infusion has been shown to be technically feasible and safe in patients with Addison's disease. A daily dose of about 10 mg/meter squared of body surface area/day, which is close to the estimated daily requirements, restores the circadian variation and normal levels of salivary cortisol in most patients.[9] Dehydroepiandrosterone (DHEA) is a major circulating adrenal steroid and substrate for peripheral sex hormone biosynthesis. The dose of DHEA is 25–50 mg/day. Daily oral administration of DHEA in physiological dosage for 12 months normalizes serum DHEA levels and has positive psychological effects. However, the dosage of DHEA may require adjustment in females and in elderly individuals.[10]

Acute adrenal insufficiency occurs is in up to 95% of critically ill patients and studies have demonstrated that corticosteroid therapy resulted in: decreased mortality and a significant survival benefit due to improved reversal of septic episode, restoration of hemodynamic stability and attenuation of systemic inflammatory response. Multiple endocrine defecits e.g. hypothyroidism and hypoadrenalism have been described in critically ill patients.[7] Patients with a baseline total cortisol level <10 ug/dl or cortisol increment after cosyntropin <9 ug/dl are very likely to have adrenal insufficiency.[8] Adrenal insufficiency is usually encountered in the late stages of polymicrobial sepsis. Its incidence is 53%–54% in patients with septic shock. The recognition of adrenal insufficiency and interventions to improve adrenal responsiveness may be beneficial in improving the outcome during late sepsis.[6,7]

Adrenal involvement has been reported in 20%–25% of patients with non-Hodgkin lymphoma, with secondary involvement in 4% as assessed by CAT scan and in 25% of patients at postmortem examination.[4,5] Addison's disease may be an early manifestation of adrenal lymphoma or relapse of a prior lymphoma, despite the presence of normal or slightly enlarged adrenal glands. In patients with prior history of lymphoma presenting with adrenal insufficiency, clinicians should consider malignant lymphoma of the adrenal gland as part of the differential diagnosis.[5] Primary adrenal lymphoma is an extremely rare entity and adrenal insufficiency is a common complication of this form of lymphoma.[4] Early diagnosis and management of adrenal insufficiency prior to staring cytotoxic chemotherapy may improve outcomes.[5]

Survival rates have improved in patients with cancer and consequently endocrine problems are increasingly recognized.[11] Endocrine glands are usually resistant to irradiation.[12] Deficiencies in secretion of anterior pituitary hormones ranging from subtle to complete develop following cranial radiation damage to the hypothalamic-pituitary axis, the severity and frequency of which correlate with the total radiation dose delivered to this axis and to the length of follow up.[11,13] There is evidence that chemotherapy may potentiate the effect of radiation on pituitary function, but there is no conclusive evidence that chemotherapy alone results in neuroendocrine dysfunction.[11] Radiation-induced anterior pituitary hormone deficiencies are irreversible and progressive. Therefore, regular testing is mandatory to ensure timely diagnosis and early hormone replacement therapy.[13] The hypothalamic-pituitary-adrenal axis may be affected relatively late by irradiation. No damage to this axis was reported following low doses of irradiation (18–24 Gy) in the treatment of ALL after 10 years of follow up. However, subtle abnormalities were reported following high doses of radiation used in the treatment of brain tumors after a similar period of follow up.[11]

Allogeneic HSCT has become a successful therapeutic modality for various hematologic malignancies and is usually performed in young patients with a long-life expectancy e.g. patients with ALL in CR1 or CR2.[14,15] In patients subjected to HSCT and despite the use of fractionated TBI in the conditioning therapies, endocrine dysfunction has been reported in up to 80% of patients on long term follow up. Growth hormone deficiency has occurred in 48%, thyroid dysfunction in 16% while hypoadrenalism has been reported in only 6.5% of patients.[15] Other studies in patients with hematologic malignancies receiving busulphan and cyclophosphamide conditioning therapies have shown high prevalence of endocrine dysfunction developing years after allogeneic HSCT. Ovarian insufficiency has been reported in 95% of patients, thyroid dysfunction in 47.5% and adrenal dysfunction in 10% of patients. In the latter study, thyroid and adrenal impairements have been reported as late events suggesting that immunosuppressive therapies and immune system derangement may play a role in the development of endocrine dysfunction after allografting.[14] Therefore, recipients of allogeneic HSCT require long-term endocrine follow up and a multidisciplinary approach regardless the type of conditioning therapy administered.[14,15]

The patient presented had a number of predisposing factors for the development of hypoadrenalism including: having a chronic debilitating illness, prior steroid therapy and recurrent infective episodes. Acute adrenal insufficiency was precipitated by TBI used in the conditioning therapy prior to HSCT. The severe dizziness and the significant postural hypotension were the clues to the diagnosis of Addisonian crisis. The diagnosis of adrenal insufficiency was confirmed by: finding a low baseline serum cortisol level, having a positive short synacthen test and responding well to corticosteroid therapy. The early diagnosis and the prompt corticosteroid replacement therapy not only controlled his acute Addisonian crisis, but also helped the patient to overcome the subsequent stresses successfully.

Conclusion

Radiotherapy is used in the treatment of malignant disorders and in the conditioning therapy prior to certain forms of HSCT. Radiotherapy has been associated with the development of chronic adrenal insufficiency. Patients with acute leukemia and recipients of HSCT who have some predisposing factors for the development of hypoadrenalism e.g. prolonged corticosteroid therapy and recurrent infections may develop acute adrenal insufficiency in the presence of new stressful events e.g. TBI. We recommend systemic testing of the endocrine function not only prior to HSCT but also at regular intervals in the post-transplant period.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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