

# Chemotherapy-Induced Adrenal Crisis

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## Citation

T Grenader, L Shavit. *Chemotherapy-Induced Adrenal Crisis*. The Internet Journal of Oncology. 2004 Volume 3 Number 1.

## Abstract

Toxicity of chemotherapy and radiotherapy may be consistent with severe stress in patients on chronic steroid therapy, and vomiting is responsible for pause in chronic steroid therapy. We describe two patients on chronic steroid therapy who received adjuvant chemotherapy and developed hypotensive shock. Both patients rapidly recovered after intravenous hydrocortisone was given.

## INTRODUCTION

The stress-induced hypotensive crisis is a life-threatening manifestation of adrenal insufficiency, with a rapidly fatal course without treatment (from shock, hypoglycaemia and/or hyperkalaemia).

In patients with chronic adrenal insufficiency, an overall risk of adrenal crisis needing hospital admission is 3.3 per 100 patient-years. Toxicity of chemotherapy and radiotherapy may be consistent with severe stress in patients on chronic steroid therapy. It may trigger Addisonian crisis if timely and adequately stress related dose adjustment are not performed.

We describe two patients on chronic steroid therapy who received adjuvant chemotherapy and developed hypotensive shock. Both patients rapidly recovered after intravenous hydrocortisone was given suspecting an acute adrenal crisis as a cause of his severe illness.

## CASE ONE

A 50-year old man was admitted to the oncology department with a one day history of fever. His medical history was remarkable for transsphenoidal hypophysectomy due to pituitary adenoma 10 years earlier. His chronic medications were prednisone 5 mg and levothyroxine 100 microgram.

Three months prior to his current admission he was diagnosed as suffering from rectal carcinoma and underwent total mesorectal excision. The pathological investigation showed well differentiated adenocarcinoma with invasion to the fat tissue. The margins were free of tumor and 11 dissected lymph nodes were free of metastases. In the perirectal fat tissue, there were two free metastases of adenocarcinoma measured 0.8 cm each.

Six weeks after surgery adjuvant chemoradiotherapy was started. He received combined radiotherapy (45 Gy in fractions of 1.8 Gy for 5 weeks) with 5-FU (500 mg/m<sup>2</sup> per day) as a rapid IV infusion days 1 to 5 and 5-FU (600 mg/m<sup>2</sup>), leucovorin (50 mg/m<sup>2</sup>) on days 15,22,29.

On the last day of radiotherapy he started suffering from subfebrile temperature. He denied chills, diarrhea, abdominal pain, respiratory or urinary symptoms.

On admission the patient was alert. His blood pressure was 95/62 mm Hg, pulse was 90 beats per minute, body temperature was 38°C. Lung, heart, abdominal and skin examination was normal.

The blood tests demonstrated severe leucopenia (0.9x10<sup>6</sup>/liter), severe neutropenia (0.2 x10<sup>6</sup>/liter), normal hemoglobin (13.5gramm%, MCV 82), normal platelets count (265x10<sup>9</sup>/liter). Blood electrolytes, renal and liver function tests were normal.

Toxicity of chemoradiotherapy was diagnosed. Intravenous fluids, intravenous antibiotics ( piperacilline, cefamesine and ciprofloxacin) and subcutaneous G-CSF were initiated. Stress-related dose adjustment of prednisone was not performed.

Twelve hours later the patient developed severe vomiting and diarrhea. On physical examination the patient was in shock with blood pressure 60/20, pulse rate 140 per minute, temperature was 39.6, poor peripheral perfusion, distended and very tender abdomen with peritoneal signs and complete lack of bowel sounds. Plain film of the abdomen demonstrated distended bowel without air-fluid levels. The blood tests revealed neutropenia and modest hyponatremia

(131 mmol/liter) and hypokalemia (3.3 mmol/liter). Adrenal crisis with paralytic ileus was diagnosed. Intravenous hydrocortisone (100mg x3/d) and intravenous fluid commenced. The patient recovered completely during the next six hours, his blood pressure rose and the abdominal pain, vomiting and diarrhea settled.

The hydrocortisone was gradually reduced and in three days he was switched to oral prednisone (10mg x1/d).

The patient was discharged in good health condition a few days later.

### CASE TWO

A 61-year-old woman underwent right breast lumpectomy and sentinel lymph node dissection for breast cancer, 1.5 cm in size. The pathological examination revealed infiltrating duct carcinoma grade 2. Sentinel lymph node was free of metastasis. According to the classification of TNM, the disease was stage II.

Abdominal ultrasound, performed for breast cancer staging, revealed a large mass of 12 cm in diameter in the right adrenal. Right adrenalectomy was performed. Histological examination of this tumor revealed adrenocortical carcinoma with large areas of necrosis and cystic degeneration. The tumor was present beyond the capsule and surgical margins.

This patient's medical history was remarkable for rheumatoid arthritis. Her chronic medicaments were prednisone 5mg once daily and methotrexate 7.5 mg once weekly.

Because of the high risk of recurrence of adrenocortical carcinoma, adjuvant chemotherapy (adriamicin, etoposid and cisplatin) was initiated. On day 5 from start of chemotherapy she began suffering from vomiting and general weakness. During the next week her vomiting worsened. Physical examination revealed emaciation with dry skin. She was hypotensive with blood pressure 85/45 mmHg and had prominent muscle weakness.

Laboratory findings included plasma sodium of 127mEq/l (normal: 135–145 mEq/l), potassium 4.9mEq/l (normal: 3.5–5.0 mEq/l), BUN 36 mg/dl (normal: 3.0–20.0 mg/dl), and creatinine 1.3 mg/dl (normal: 0.5–1.2 mg/dl). According to her clinical picture and typical electrolytes changes, the diagnosis of Addisonian crisis was presumed. The plasma cortisol level was obtained and was given. The patient completely recovered during next few hours. The plasma cortisol level was < 50 nmol/L (normal: 165–680 nmol/L).

The patient refused to continue chemotherapy.

### DISCUSSION

We reported two patients on long term glucocorticoid therapy who received adjuvant chemotherapy and developed adrenal crisis. The first patient suffered from chronic adrenal insufficiency due to previous hypophysectomy and was on chronic steroid replacement therapy. Lack of steroid dose adjustment for stress together with chemoradiation toxicity induced acute adrenal crisis with typical clinical presentation of shock, muscle weakness, abdominal pain and vomiting.

The second patient received chronic prednisone therapy for rheumatoid arthritis. The cause of chronic adrenal insufficiency was suppression of the hypothalamic-pituitary-adrenal axis. After chemotherapy the patient suffered from vomiting and didn't receive maintenance of prednisone. Rapid and complete recovery of both patients after intravenous hydrocortisone administration confirms the diagnosis of Addisonian crisis.

Diagnosis of adrenal crisis may be masked in cancer patients receiving chemotherapy. Vomiting, weakness, diarrhea and electrolyte unbalance may be attributed to adverse effects of chemotherapy or non-specific symptoms of cancer. A short course of steroid therapy is a part of some chemotherapeutic regimens. Chemotherapy toxicity may be associated with severe stress in patients with chronic adrenal insufficiency, and vomiting is responsible for pause in chronic steroid therapy.

Despite the frequency of chronic steroid treatment in cancer patient, we found only one report describing Addisonian crisis in a patient who received chemotherapy. This patient with bladder cancer metastatic to adrenal gland presented as acute adrenal insufficiency with hypovolemic shock. He received first course of MVAC therapy with hydrocortisone and was discharged with maintenance therapy of oral prednisone 15 mg once daily. After each of the two courses of chemotherapy he received, he was admitted to the emergency room with symptoms of acute adrenal insufficiency during nadir period despite steroid maintenance therapy.

Oncologist should be aware of the possibility of acute adrenal crisis in patients receiving long term glucocorticosteroid therapy, consider timely and adequately adjustment of the steroid dose for stress to avoid development of life-threatening complication of acute adrenal insufficiency.

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