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Case Report

Pathology Section

An Autopsy of Acute Adrenal Insufficiency Resulting from Infarction of Both Adrenal Glands, in a Pregnant Woman with Metastatic Carcinoma of the Breast

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ABSTRACT

Acute Adrenal Insufficiency (AAI) is a life-threatening medical emergency, associated with high mortality, and requires early diagnosis and prompt management. This is an unusual case report of a 34-year-old female who was diagnosed with breast cancer, in the second trimester of pregnancy. She presented at 33 weeks gestation, in the emergency services, with convulsions, weakness, altered sensorium and high-grade infiltrating duct carcinoma of breast with liver metastasis. She had also received a single cycle of chemotherapy with adriamycin and cyclophosphamide, at 33 weeks of pregnancy. Her condition deteriorated within 12-16 hours, and she developed abdominal pain, generalised weakness and convulsions. The patient was induced into labour, which was complicated, and delivered a still born male child. She also developed acute kidney injury and severe electrolyte imbalance, and died within four days of admission. A complete postmortem examination was performed where the cause of death was AAI following infarction of both adrenal glands in a background of metastatic carcinoma of the breast. It is strongly suspected that chemotherapy with adriamycin and cyclophosphamide is the primary cause of AAI in the present case. However, the etiology could also be multifactorial as factors like, sepsis, intrauterine foetal death and Disseminated Intravascular Coagulation (DIC) were also present.

Keywords: Adrenal crisis, Adriamycin, Chemotherapy, Cyclophosphamide, Invasive breast carcinoma

CASE REPORT

A 34-year-old female, a known case of breast cancer, with 33 weeks of pregnancy, was referred to the emergency services of our tertiary care hospital. She had a short history of convulsions, weakness and altered sensorium prior to admission. She did not have any oedema, proteinuria or hypertension.

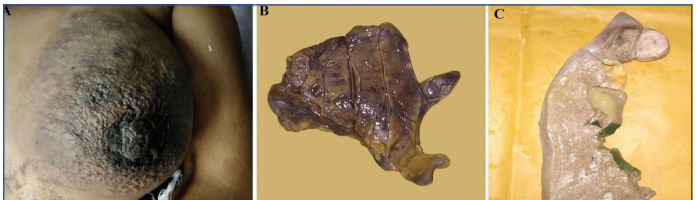
The patient was induced into labour, which was complicated with foetal distress and delivered with outlet forceps. At the time of labour, the foetal heart rate dropped to 80 beats/minute, a tight loop of cord with two knots was seen around the neck of the fetus, and the liquor was meconium stained. She delivered a 2.2 kg, stillborn, male fetus. Placenta was delivered spontaneously and completely.

At six months of pregnancy, the patient noticed lumps, in her left breast and left axilla. Ultrasonography done showed a large breast lump measuring 5×2 cm, Breast Imaging Reporting and Database System (BIRADS) Category V, with satellite lesions in the left axilla. Abdominal sonography revealed hepatic lesions, strongly suggestive of metastasis. Biopsy and histopathology of the breast lump revealed an infiltrating ductal carcinoma, Not Otherwise Specified (NOS) Grade 3. She was then referred to an Oncology Institute at 33 weeks pregnancy, and treated with one cycle of chemotherapy which included adriamycin and cyclophosphamide, following which she developed generalised weakness and dull abdominal pain, within 12-16 hours.

The haematological investigations revealed haemoglobin 9.2 gm%, total leucocyte count of 5200/mL, platelets 1.9 lac/mL. Biochemical investigations were as follows: blood urea nitrogen 92 mg/dL, serum creatinine 4.0 mg/dL, serum uric acid 17.5 mg/dL, serum calcium 15.7 mg/dL, serum sodium was 132 mEq/l, serum potassium was 2.9 mEq/L. A nephrology opinion was sought and an opinion of acute kidney injury with hypercalcaemia, hypokalemia, hypermagnesemia and hyperuricaemia was made, and corrections for the same were given. The patient however progressed into shock, despite medications and Sustained Low Effusion Dialysis (SLED) was started. Her condition worsened, and her coagulation profile was altered with fibrinogen raised to >500 mg/dL, fibrin degradation products were raised to >80 mg/dL and D-dimer was raised to 4.1 mg/dL. Prothrombin time was 9.1 sec (control: 9.9 sec, INR: 0.9), activated infiltrating ductal thromboplastin time was 17.1 (control: 26.0). The clinical diagnosis was acute kidney injury, DIC, with left breast carcinoma, in post partum period.

The patient had a ward stay of four days at the hospital, during which her general condition kept deteriorating, and she succumbed to the illness. A complete autopsy was performed. The left breast showed a firm tumour of 5×2 cm. The entire skin of the breast had a blackish discolouration with peau d'orange and nipple and areola were unremarkable [Table/Fig-1a]. A left axillary mass of 2.5×2 cm was also seen. Both the adrenal glands were moderately enlarged in size, weighing 8 gm each, and were haemorrhagic [Table/Fig-1b]. There was no pallor, oedema, icterus, cyanosis, clubbing and no free fluid in the pleural cavity or abdominal cavity.

The liver weighed 2.2 kg and showed a nodule measuring 2.2 cm in diameter in the inferior portion of the left lobe [Table/Fig-1c]. Kidneys were enlarged in size, each weighing 210 gm, with a few superficial scars. Both lungs were congested, while the heart, spleen, brain, intestines, uterus and ovaries, were unremarkable.

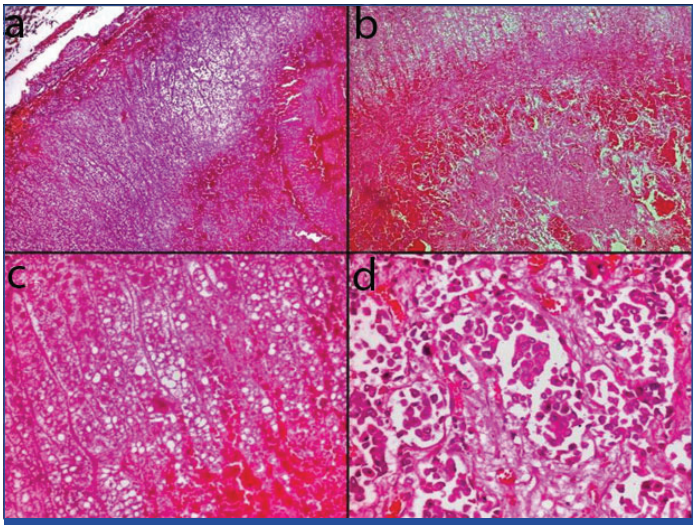


[Table/Fig-1]: a) Lump in the left breast with overlying blackish discolouration of skin. b) Enlarged and infarcted right adrenal gland weighing 8 gm. c) Metastatic nodule of 2×2 cm diameter on the left lobe of the liver.

Both the adrenal glands showed complete infarction of the adrenal cortex and medulla, with haemorrhages and venous thrombi in the glands as well as the surrounding peri-adrenal fat. Focal calcification was also seen in both adrenal glands [Table/Fig-2a-c].

The liver showed a metastatic nodule with similar histomorphological features. The kidneys showed patchy tubular necrosis and mild chronic pyelonephritis. The uterus showed areas of hemorrhage within the myometrium and congested vasculature. The rest of the organs were within normal histological limits.

Histopathology of the breast lump showed a high-grade infiltrating duct carcinoma, NOS, Grade 3 [Table/Fig-2d]. The tumour was composed of sheets of malignant ductal epithelial cells with hyperchromatic, pleomorphic nuclei, prominent nucleoli and scant cytoplasm. Many tumour giant cells and brisk mitoses were seen. The final autopsy diagnosis was primary AAI following infarction of both adrenal glands, in a background of invasive carcinoma of the breast with liver metastasis.



[Table/Fig-2]: a) Low power view of the right adrenal gland showing complete infarction of the cortex and medulla (H&E x 100); b) Low power view of the left adrenal gland showing complete infarction and haemorrhages in the cortex and medulla (H&E x100); c) High power view of the adrenal gland showing coagulative necrosis of both, the adrenal cortex and medulla (H&E x400); d) High power view of the breast tumour showing high grade infiltrating ductal carcinoma (H&E x400).

DISCUSSION

Primary AAI is an uncommon, but life-threatening medical emergency, requiring prompt diagnosis and emergency treatment. It results from insufficient levels or absence of hormone cortisol and mineralocorticoids. Chronic adrenal insufficiency was first described by Thomas Addison, in 1855, in patients with adrenal failure due to tuberculosis [1].

AAI can present with a variety of nonspecific symptoms and its diagnosis requires a high index of clinical suspicion. Symptoms of AAI include nausea, abdominal pain, vomiting, diarrhoea, severe lethargy, fever, convulsions, syncope, hypotension, shock etc. [2,3]. Biochemical abnormalities include hyponatremia, hyperkalemia, hypercalcaemia and hypoglycaemia [2,3].

The aetiology of AAI is complex with common precipitating factors like gastrointestinal illness, physical stress, pain, dehydration, and post-surgery etc promoting its development [1]. Chemotherapy and pregnancy are lesser-known precipitating factors leading to AAI [1,4]. In present case, chemotherapy is a significant precipitating factor, since the symptoms of adrenal insufficiency developed within 12-16 hours of chemotherapy. The present patient also had other predisposing factors like intrauterine foetal death, sepsis, and DIC, which was evident in the deranged coagulation profile, as well as the extensive fibrin thrombi in both the infarcted adrenal glands and periadrenal tissue. In addition, the presence of an underlying carcinoma breast with metastasis to the liver, leading to sepsis and DIC, has also to be kept in mind with this case. Severe coagulopathies have been associated with adrenal vein thrombosis and haemorrhagic infarction as was seen in our case [5]. In present case, the aetiology could also be multifactorial with pregnancy, DIC, intra-uterine foetal death, sepsis and chemotherapy (adriamycin and cyclophosphamide) given to the patient. Despite extensive search in English literature, no case of AAI has been reported following use of these two chemotherapy agents. Her blood pressure was within the normal range throughout the ward stay and with the absence of proteinuria, hence eclampsia was ruled out.

Diagnosis of AAI, in general, is based on the demonstration of inappropriately low cortisol secretion and the diagnosis is made by the ACTH stimulation test. In general, serum cortisol level determined at 8:00 am at <3 mcg/dL strongly supports the diagnosis of AAI [6]. The diagnostic cut-offs for adrenal insufficiency in pregnancy are not well established and the diagnosis is difficult, because of the altered endocrine changes, and the symptomatology of adrenal insufficiency closely resembling the symptoms of pregnancy [7]. Normal cortisol levels vary during the various trimesters of pregnancy and in third trimester of pregnancy, the level is 12-50 mcg/dL. Peak cortisol levels are higher in pregnancy following the ACTH stimulation test [8]. Cortisol levels in this patient were not done, as a diagnosis of acute adrenal failure was not suspected.

The principle of management of adrenal crisis is steroid replacement, and intravenous fluid resuscitation with isotonic saline to correct the hypovolemia and hyponatremia [9]. This patient was given dexamethasone, thiamine, metronidazole, vancomycin, dextrose, calcitonin, vasopressin and dopamine and replacement for electrolytes with SLED.

Acute adrenal crisis can develop only when >90% of the adrenal cortex is destroyed. Histopathological examination in our case showed complete infarction of both adrenal glands, with no viable adrenal tissue seen. Extensive thrombosis of the adrenal vasculature was also seen. Adrenal insufficiency is rare in pregnancy and it may be associated with significant maternal and foetal mortality, if left untreated, as was seen in our case [9].

CONCLUSION(S)

Acute Adrenal Insufficiency (AAI) is a treatable disease but a high level of clinical suspicion and prompt treatment is required for its management. In view of the sequence of events, chemotherapy with adriamycin and cyclophosphamide is strongly suspected to be the cause of AAI in this case. Other factors like sepsis, intra-uterine foetal death and DIC could also be significant contributors to AAI.

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