BRIEF REPORT

Acute Adrenal Insufficiency in Association With Pancreatic Carcinoma

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Addison's disease secondary to metastatic cancer to the adrenal gland is underdiagnosed. Prompt diagnosis and treatment is essential and could enhance the quality of life. Cases of adrenal insufficiency produced by metastatic carcinoma are unusual, despite the frequency of carcinomatous metastases to the adrenal glands. The clinical features of adrenal insufficiency are relatively nonspecific and can be easily overlooked in a patient with a malignant neoplasm. We report herein the case of a middle-aged man who presented with adrenal insufficiency in association with pancreatic carcinoma. To our knowledge, this is the first reported case of adrenal insufficiency occurring with adenocarcinoma of the pancreas.

REPORT OF A CASE

The patient, a 62-year-old white man, was admitted to the hospital for evaluation of increasing abdominal pain and jaundice. Before admission, he had undergone computed tomography of the abdomen, which revealed bilateral adrenal enlargement. He was reportedly doing well until approximately 1 month before admission when be began complaining of malaise, nausea, vomiting, and abdominal pain. He denied associated weight loss, anorexia, hematemesis, or melena. The initial impression of his family physician was a flulike syndrome, and he was treated conservatively as an outpatient. One week before admission, when his condition did not improve, the computed tomographic scan was obtained. The patient's medical history was unremarkable for a malignant neoplasm. He denied alcohol abuse but had an 80-pack-year smoking history. He had no known allergies and was taking no medications.

On physical examination, the patient was obviously icteric and appeared 10 years older than his stated age. He denied postural dizziness. Vital signs were stable, including a blood pressure that was 100/60 mm Hg. Orthostasis was not assessed. The patient was 173 cm tall and weighed 74 kg. He was afebrile. No skin hyperpigmentation was noted. Head, eyes, ears, nose, and throat were unremarkable except for scleral icterus. The remainder of the physical examination findings were normal with the exception of the abdominal examination findings. His abdomen was diffusely tender without rebound. Bowel sounds were normal and ascites was absent. The gallbladder was easily palpable but not tender. No other masses or organ enlargement was found. The prostate was normal and the stool was guaiac negative.

On admission, the patient had a hemoglobin level of 120 g/L, a white blood cell count of 13.7×10^9/L, and a platelet count of 572×10^9/L. Serum electrolytes, glucose, amylase, serum urea nitrogen, and creatinine levels were within normal limits. The total bilirubin level was 156 μmol/L (9.1 mg/dL); alanine aminotransferase, 362 U/L; aspartate aminotransferase, 572 U/L; and alkaline phosphatase, 872 U/L. Urinalysis revealed the presence of bile without urobilinogen. Repeated abdominal com-

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puted tomography on admission revealed dilated common bile and pancreatic ducts with the suggestion of a mass at the head of the pancreas. Hypodense areas were noted throughout the liver parenchyma. Bilateral adrenal enlargement was again noted.

It was believed that the patient had pancreatic cancer with metastases to the liver and was not a surgical candidate. He was treated conservatively with analgesia and diet as tolerated, which, for the most part, was unsuccessful owing to his persistent nausea, vomiting, and abodminal pain presumed secondary to the biliary obstruction. Five days after admission, the patient had a near syncopal episode while walking to the bathroom. He was found to be hypotensive with a blood pressure of 60/40 mm Hg.

Laboratory studies revealed markedly abnormal electrolyte values with a sodium level of 115 mmol/L; potassium level, 6.2 mmol/L; chloride level, 80 mmol/L; and bicarbonate level, 25 mmol/L. Adrenal insufficiency was presumed, and 100 mg of hydrocortisone hemisuccinate was immediately administered intravenously, normalizing the patient's blood pressure. A serum cortisol level determined before the administration of hydrocortisone was low normal at 165 nmol/L, and a corticotropin level determined on the same sample was increased to 36 pmol/L.

The patient's abdominal complaints, including the nausea, vomiting, and abdominal pain, diminished with hydrocortisone and fludrocortisone (Florinef) acetate supplementation. His hyponatremia and hyperkalemia also resolved shortly after steroid replacement. The patient's hospital course, however, was complicated by sepsis, and he died on the 14th hospital day. The cause of the sepsis was believed to be ascending cholangitis secondary to the biliary obstruction and not a result of malignancy-reduced immunity or hydrocortisone administration. At autopsy, a large adenocarcinoma was found in the head and body of the pancreas. The adrenal glands were entirely replaced by tumor, and the small bowel and retroperitoneal lymph nodes were infiltrated with metastases.

COMMENT

Addison's disease refers to partial or complete adrenocortical insufficiency. Autoimmune and granulomatous diseases are the leading causes of Addison's disease in the general population.[1,2] Drug-induced adrenal insufficiency can occur with ketoconazole (Nizoral), aminoglutethimide (Cytadren), mitotane (*o,p'*-DDD), metyrapone, etomidate, suramin, and interleukin 2.[3-8] Rifampin, phenytoin, and phenobarbital accelerate catabolism of cortisol, which can precipitate adrenocortical failure in partially compromised individuals.[1] Other causes include infections,[1,9] hemorrhage/thrombosis,[10] hemochromatosis,[1] amyloidosis,[11] acquired immunodeficiency syndrome,[12] adrenoleukodystrophy/adrenomyeloneuropathy,[13] familial glucocorticoid deficiency,[14] surgery,[15-17] and metastatic disease (most commonly adenocarcinomas).

The frequency of metastases to the adrenal gland in autopsy series of patients with cancer ranges from 8.6% to 27%,[18,19] the most common primary tumors being lung,[20-28] gastric,[23,29,30] colorectal,[23,31-33] esophageal,[23,29,34] and breast.[35,36] As many as 58% of patients with breast

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carcinoma and 36% with lung cancer have been found at autopsy to have adrenal metastases.[37] Less-common malignant neoplasms associated with Addison's disease include melanoma,[38] lymphoma,[39-44] prostate,[45,46] renal cell,[47,48] transitional cell,[49] jejunal,[50] seminoma,[51] carcinoid,[52] and adrenocortical carcinoma.[53] Pancreatic carcinoma metastasizes to the adrenal glands, but adrenal insufficiency has not been mentioned in previous reports.[54] The **Table** summarizes the causes of primary adrenal insufficiency.

The clinical features of Addison's disease are relatively nonspecific and can be ascribed to a number of disorders, thus making the diagnosis difficult.[55,56] Symptoms do not usually occur until approximately 90% of the adrenal gland is destroyed. Vague constitutional symptoms such as fatigue, malaise, weight loss, and weakness occur in most addisonian patients. Hypotension and orthostasis are found in 80% to 90% of cases, but fewer than 20% of these patients complain of postural dizziness or syncope. Hyperpigmentation is common and most noticeable over the extensor surfaces of the hands, knuckles, elbows, and palmar creases as well as on mucous membranes. Abdominal

Causes of Primary Adrenal Insufficiency

Autoimmune	
	Polyglandular autoimmune I, II
Infections	
	Tuberculosis, blastomycosis, coccidioidmycosis, histoplasmosis, cryptococcosis, human immunodeficiency virus associated
Drugs	
	Decreased synthesis: metyrapone, aminoglutethimide, mitotane, etomidate, ketoconazole, suramin; increased catabolism: rifampin, dilantin, phenobarbital, interleukin 2
Infiltrative	
	Hemochromatosis, amyloidosis, sarcoidosis
Adrenal hemorrhage	
	Waterhouse-Friderichsen syndrome, anticoagulation, antiphospholipid antibodies, lupus anticoagulant
Familial	
	Familial glucocorticoid deficiency, adrenoleukodystrophy, adrenomyeloneuropathy
Surgical	
Metastatic disease	
	Lung, esophagus, gastric, breast, colorectal, melanoma, lymphoma, prostate, renal cell, seminoma, jejunal, carcinoid, pancreatic, adrenocortical carcinoma, transitional cell

pain, anorexia, nausea, vomiting, and diarrhea are frequent gastrointestinal symptoms associated with this disease. Laboratory abnormalities include hyponatremia, hyperkalemia, hypoglycemia, mild azotemia, mild metabolic acidosis, and lymphocytosis. Hypercalcemia is an uncommon feature sometimes seen in these patients.

IN THE patient described herein, constitutional, gastrointestinal, and biochemical manifestations of Addison's disease were present in association with pancreatic adenocarcinoma. Infiltration of the adrenal glands by tumor metastases is a common occurrence. This is believed to be due in part to the abundant sinusoidal blood supply of the adrenal gland and also the local concentration of corticosteroids that promotes the implantation of metastases due to altered cell-mediated immunity.

The question arises as to how many patients with adrenal metastases actually are identified with adrenal insufficiency. Clinical adrenal insufficiency from tumor metastases rarely occurs unless there is extensive bilateral adrenal involvement. Retrospective and prospective studies have found that up to one third of patients found to have bilateral adrenal gland metastases secondary to neoplastic disease will ultimately develop Addison's disease.[57,58] There are very few reports of Addison's disease as the presenting feature of an underlying malignant disease with adequate biochemical documentation of adrenal hypofunction.[23,59-61]

The diagnosis of Addison's disease may often be delayed or missed entirely because of the nonspecific nature of the symptoms. This is particularly true in patients with established malignant neoplasms, because these symptoms are often attributed to the malignant neoplasm itself. It is important, therefore, that computed tomography of the adrenal glands be considered part of the malignancy evaluation, especially with those malignant neoplasms that are histologically adenocarcinomas. Any patient found to have radiographic evidence of enlarged adrenal glands should undergo endocrine testing regardless of whether symptoms of adrenal insufficiency are currently evident. Even if there is no biochemical evidence of adrenal insufficiency, mineralocorticoid replacement therapy should be considered since the natural history of adrenal metastases in a substantial number of these patients includes the development of adrenal insufficiency. A partially compromised patient in the basal state could rapidly decompensate during any degree of stress.

A low or "normal" random serum cortisol level can suggest adrenal insufficiency particularly in the presence of an acute illness. However, this is not always diagnostic of adrenal insufficiency, and a cosyntropin stimulation test can be done to confirm the diagnosis.[62]

Cosyntropin is a synthetic corticotropin analogue. Serum cortisol levels are measured before and 1 hour after administration of 250 μg of cosyntropin. A normal response is an increment in the plasma cortisol level of 278 mmol/L or a peak level greater than 490 mmol/L. Administration of hydrocortisone should result in improvement within 24 hours of administration. A cosyntropin stimulation test was not performed in our patient secondary to the fact that the increased corticotropin level in association with a low-normal cortisol level supported the diagnosis. It was believed that the patient's hypotension served as an endogenous cosyntropin stimulation test.

Addison's disease secondary to metastatic cancer to the adrenal glands is probably underdiagnosed. Because of the frequency of metastases to the adrenal glands, visualization of the adrenals should be considered in the workup of malignant neoplasms, particularly adenocarcinoma. In patients with bilateral adrenal enlargement, screening for adrenal insufficiency with a cosyntropin stimulation test may be indicated regardless of the presence or absence of symptoms. Empiric mineralocorticoid therapy is not an unreasonable alternative. This would avoid the cost and potential misdiagnosis of the cosyntropin stimulation test and eliminate the need for further testing in those patients with normal results. Prompt recognition and treatment will avert potentially life-threatening adrenal insufficiency and could enhance the quality of the patient's life.

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REFERENCES

1. Werbel SS, Ober KP. Acute adrenal insufficiency. *Endocrinol Metab North Am.* 1993;22:303-328.
2. Derosa G, Corsello SM, Cecchini L. Clinical study of Addison's disease. *Exp Clin Metab.* 1987;90:232-242.
3. White MC, Kendall-Taylor P. Adrenal hypofunction in patients taking ketoconazole. *Lancet.* 1985;1:44-45.
4. Murray R, Pitt P. Low-dose aminoglutethimide without steroid replacement in the treatment of post-menopausal women with advanced breast cancer. *Eur J Cancer Clin Oncol.* 1985;21:19-22.
5. Burke CW. Adrenocortical insufficiency. *Clin Endocrinol Metab.* 1985;14:947-976.
6. Wagner RL, White PF, Kan PB, Rosenthal MH, Feldman D. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. *N Engl J Med.* 1984;310:1415-1421.
7. Stein CA, Thomas LR, McAtee N, Myers CE. Sumarin: an anticancer drug with a unique mechanism of action. *J Clin Oncol.* 1989;7:499-508.
8. WanderMolen LA, Smith JW, Longo DL, Steis RG, Kremers P, Sznol M. Adrenal insufficiency and interleukin-2 therapy. *Ann Intern Med.* 1989;111:185.
9. Bosworth C. Reversible adrenocortical insufficiency in fulminant meningococcemia. *Arch Intern Med.* 1979;139:823-824.
10. Rao RH, Vagnucci AH, Amico JA. Bilateral massive adrenal hemorrhage: early recognition and treatment. *Ann Intern Med.* 1989;110:227-235.
11. Danby P, Harris KPG, Williams B, Feehally J, Walls J. Adrenal dysfunction in patients with renal amyloid. *Q J Med.* 1990;281:915-922.
12. Aron DC. Endocrine complications of the acquired immunodeficiency syndrome. *Arch Intern Med.* 1989;149:330-333.
13. Nejad-Sadeghi A, Senior B. Adrenomyeloneuropathy presenting as Addison's disease in children. *N Engl J Med.* 1990;322:13-16.
14. Spark RF, Etzkorn JR. Absent aldosterone response to ACTH in familial glucocorticoid deficiency. *N Engl J Med.* 1977;297:917-920.

15. Henrich WL, Goldberg J, Lucas M, Gabow P. Adrenal insufficiency after unilateral radical nephrectomy. *Urology.* 1976;8:584-585.
16. McLeod MK. Complications following adrenal surgery. *J Natl Med Assoc.* 1991; 83:161-164.
17. Angermeier RW, Montie JE. Perioperative complications of adrenal surgery. *Urol Clin North Am.* 1989;16:597-606.
18. Abrams HL, Spiro R, Goldstein N. Metastases in carcinoma: analysis of 1000 autopsied cases. *Cancer.* 1950;3:74-85.
19. Bullock WK, Hirst AE. Metastatic carcinoma of the adrenal. *Am J Med Sci.* 1953;226:521-524.
20. Payne KD, Levine SN, Franco DP, Giyanani VL. Adrenal insufficiency due to metastatic lung carcinoma and shown by abdominal CT scan. *South Med J.* 1984;77:1592-1593.
21. Pagani JJ. Non-small cell lung carcinoma adrenal metastases. *Cancer.* 1984; 53:1058-1060.
22. Cowan JD, Kies MS, Mulgrew PJ, Cerezo L. Addison's disease due to metastatic carcinoma. *South Med J.* 1984;77:796-799.
23. Kung AWC, Pun KK, Lam K, Wang C, Leung CY. Addisonian crisis as presenting feature in malignancies. *Cancer.* 1990;65:177-179.
24. Hill GJ, Wheeler HB. Adrenal insufficiency due to metastatic carcinoma of the lung: case report and review of Addison's disease caused by adrenal metastases. *Cancer.* 1965;18:1467-1473.
25. Sheeler LR, Myers JH, Eversman JJ, Taylor HC. Adrenal insufficiency secondary to carcinoma metastatic to the adrenal gland. *Cancer.* 1983;52:1312-1316.
26. Khan A, Khan FA, Mehra S, Tafreshi M. Addison's disease due to metastatic carcinoma: the value of the CT scan. *Comput Radiol.* 1983;7:369-371.
27. Weber CL, Murphy ML. Adrenal hypofunction secondary to adrenocortical destruction by metastatic carcinoma of the lung. *J Ark Med Soc.* 1971;68:181-183.
28. Meyer JE, Halperin EC, Levene SR, Stomper PC. Adrenal insufficiency secondary to metastatic lung carcinoma: CT aided diagnosis. *J Comput Assist Tomogr.* 1983;7:1107-1108.
29. Cedermark BJ, Blumenson LE, Pickren JW, Elias EG. The significance of metastases to the adrenal gland from carcinoma of the stomach and esophagus. *Surg Gynecol Obstet.* 1977;145:41-48.
30. Leary OC, Masters JJ. Adrenal insufficiency produced by metastases from gastric carcinoma. *Ann Intern Med.* 1957;46:1161-1165.
31. Cedermark BJ, Blumenson LE, Pickren JW, Holyoke DE, Elias EG. The significance of metastases to the adrenal glands in adenocarcinoma of the colon and rectum. *Surg Gynecol Obstet.* 1977;144:537-546.
32. Black RM, Daniel GH, Coggins CH, Mueller PR, Data RE, Lichtenstein N. Adrenal insufficiency from metastatic colonic carcinoma masquerading as isolated aldosterone deficiency: report of a case and a review of the literature. *Acta Endocrinol.* 1981;98:586-591.
33. Omoigui NA, Cave WT, Chang AY. Adrenal insufficiency: a rare initial sign of metastatic colon carcinoma. *J Clin Gastroenterol.* 1987;9:470-474.
34. Hasan RI, Yonan NA, Lawson RA. Adrenal insufficiency due to bilateral metastases from oat cell carcinoma of the esophagus. *Eur J Cardiothorac Surg.* 1991;5:336-337.
35. Alpers DH, Engelman K, Foley FD. Addison's disease secondary to metastastic carcinoma of the breast. *Ann Intern Med.* 1962;57:464-467.
36. Golloway JA, Perloff B. Addison's disease secondary to adrenocortical destruction by metastatic carcinoma of the breast. *Am J Med.* 1960;28:156-158.
37. Zimm S, Gardner DF, Walsh JW, Maine CP, Ferguson RH, Smith WK. Addison's disease as the sole clinical manifestation of recurrent bronchogenic carcinoma. *South Med J.* 1981;74:1016-1018.
38. Gupta DT, Brasheld R. Metastatic melanoma. *Cancer.* 1964;17:1323-1339.
39. Gamelin E, Beldent V, Rousselet MC, et al. Non-Hodgkin's lymphoma presenting with primary adrenal insufficiency: a disease with an underestimated frequency? *Cancer.* 1992;69:2333-2336.
40. Dobnig H, Sillh H, Ohlinger W, Neubauer M, Leb G, Drejs GJ. Successful treatment of primary adrenal insufficiency due to malignant non-Hodgkin's lymphoma. *Clin Invest.* 1992;70:938-941.
41. Khan S, Raby N, Michell M. Non-Hodgkin's lymphoma confined to the adrenal glands presenting with Addison's disease. *Clin Radiol.* 1990;42:63-64.
42. Oppong FC, Brodribb AJ, Hunt AC, Ring NE. Bilateral adrenal lymphoma presenting as Addison's disease and hypercalcemia. *Eur J Surg Oncol.* 1991;17: 395-396.
43. Cares RW, Harris N, Kilman B. Addison's disease secondary to lymphomatous infiltration of the adrenal glands. *Cancer.* 1987;59:1087-1090.
44. Ihde JK, Turnbull ADM, Bajorunas DR. Adrenal insufficiency in the cancer patient: implications for the surgeon. *Br J Surg.* 1990;77:1335-1337.
45. Mirtsching BC, Freeman DA. Adrenal insufficiency and stage D carcinoma of the prostate. *South J Med.* 1992;85:196-197.
46. Navarro M, Felip E, Garcia L, et al. Addison's disease secondary to prostatic carcinoma: a case report. *Tumori.* 1990;76:611-613.
47. Goldenberg SL, Wright JE, McLoughlin MG. Metastatic renal cell carcinoma: unusual cause of Addison disease. *Urology.* 1983;22:408-409.
48. Goffman TE, Schechter GP, McKeen EA, Mariani-Costantini R, Schein PS. Renal cell carcinoma causing a selective mineralocorticoid insufficiency. *J Urol.* 1982;128:370-371.
49. Kennedy RL, Ball RY, Dixon AK, ApSimon AT. Metastatic transitional cell carcinoma of the bladder causing Addison's disease. *J Urol.* 1987;137:986-988.
50. Greene R. Addison's disease with hypoglycemia apparently due to jejunal carcinoma. *Br J Clin Pract.* 1975;29:193-194.
51. Heuson JC. Addison's disease secondary to occult metastatic seminoma. *Cancer.* 1966;19:1754-1759.
52. Bruce TA, Azmy M, Earll JM. Gastric carcinoid associated with achlorhydria, hypergastrinemia, and Addison's disease. *South J Med.* 1988;81:1595-1596.
53. Heath H, Bergevin PR. Adrenal insufficiency resulting from metastasis of nonfunction adrenocortical carcinoma. *Med Ann D C.* 1973;42:545-547.
54. Sahagian-Edwards A, Holland JF. Metastatic carcinoma to the adrenal glands with cortical hypofunction. *Cancer.* 1954;7:1232-1245.
55. Davenport J, Kellerman C, Reiss D, Harrison L. Addison's disease. *Am Fam Physician.* 1991;43:1338-1342.
56. Steer M, Fromm D. Recognition of adrenal insufficiency in the postoperative patient. *Am J Surg.* 1980;139:443-446.
57. Seidenwurm DJ, Elmer EB, Kaplan LM, Williams EK, Morris, MG, Hoffman AR. Metastases to the adrenal glands and the development of Addison's disease. *Cancer.* 1984;54:552-557.
58. Redman BG, Pazdur R, Zingas AP, Lordeo R. Prospective evaluation of adrenal insufficiency in patients with adrenal metastases. *Cancer.* 1987;60:103-107.
59. Vieweg WVR, Reitz RE, Weinstein RL. Addison's disease secondary to metastic carcinoma: an example of adrenocortical and adrenal insufficiency. *Cancer.* 1973; 31:1240-1243.
60. Rosenthal FD, Davies MK, Burden AC. Malignant disease presenting as Addison's disease. *BMJ.* 1978;1:1591-1592.
61. Mor F, Lahav M, Kipper E, Wysenbeek AJ. Addison's disease due to metastases to the adrenal glands. *Postgrad Med J.* 1985;61:637-639.
62. Speckart PF, Nicoloff JT, Bethune JD. Screening for adrenocortical insufficiency with cosyntropin (synthetic ACTH). *Arch Intern Med.* 1971;128:761-763.