CASE REPORT

Cushing's syndrome complicated by multiple opportunistic infections

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ABSTRACT. The case history of a 56-year-old man is described who suffered from severe adrenocorticotrophic hormone (ACTH)-dependent Cushing's syndrome. The clinical course was complicated by simultaneous infections with Pneumocystis carinii, Staphylococcus aureus, Candida albicans, Aspergillus fumigatus and Herpes simplex, which proved to be fatal. A study of the literature shows that opportunistic infections in endogenous Cushing's syndrome are associated with severe cortisol excess and carry a high mortality. Opportunistic infections are most prevalent in the ectopic ACTH syndrome, explained by the very high plasma cortisol concentrations in this condition. Infections with Aspergillus species, Cryptoccus neoformans, Pneumocystis carinii and Nocardia asteroides predominated. Cushing's syndrome with a very high plasma cortisol concentration causes a severe immunocompromized state. Prompt evaluation of the cause of the hypercortisolism, initiation of cortisol lowering therapy, primary prophylaxis for Pneumocystis carinii infection when plasma cortisol exceeds 2500 nmol L^{-1} and a search for concomitant infectious disease is recommended.

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INTRODUCTION

In early reports on patients with Cushing's syndrome it was already recognised that infections were part of the clinical picture (1-3). Death often occurred due to wound infections or tuberculosis (3,4). Better understanding of the syndrome and antibiotic therapy, however, led to a sharp reduction of infection as cause of mortality and morbidity (5). Infection with opportunistic pathogens has subsequently been reported in a number of patients with endogenous Cushing's syndrome (6-36). In the present report we describe a patient suffering from Cushing's syndrome with an extremely high plasma cortisol concentration who developed simultaneous infections with bacterial, viral, and fungal pathogens which proved to be fatal. This case suggests that endogenous Cushing's syndrome with very high plasma cortisol concentrations is a medical emergency which requires prompt medical treatment including anti-infectious therapy when infection is suspected.

Key-words: Cushing, infection, opportunistic.

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CASE REPORT

A 56-year-old man was transferred from another hospital to our clinic for further evaluation and treatment of Cushing's syndrome. The patient was an active and healthy man until six months before admission when he developed general malaise, sexual impotence and progressive muscle weakness. His previous medical history mentioned appendectomy at age 15 and a traumatic pneumothorax at age 45. The patient did not smoke or consume alcohol on a regular basis. Four months before admission hyperglycemia (postabsorptive glucose level 15 mmol L^{-1}) was discovered and more recently hypokalemia (2.8 mmol L^{-1}). Oral thrush also developed. On admission to our hospital a sick, confused man was seen with pronounced proximal muscle weakness. His blood pressure measured 150/100 mm Hg. The pulse was regular with a frequency of 80/min and the respiratory rate was

18/min. Rectal temperature measured 37 C. No lymphadenopathy was noted. The examination of heart, lungs and abdomen was unremarkable. The skin appeared slightly atrophic and pitting edema of the ankles existed. A small ulcer on the right index finger and two small superficial penile ulcers were found. Centripetal obesity, buffalo hump, striae and skin bleedings were absent. Laboratory evaluation demonstrated an ESR 4 mm/hr, hemoglobin 7.7 mmol L^{-1}, leukocytes 11.0 10^9 L^{-1} and differential count: 90% neutrophils with 3% bandforms, 7% lymphocytes, 2% monocytes, 1% metamyelocytes. Serum sodium was 146 mmol L^{-1}, potassium 2.9 mmol L^{-1}, chloride 103 mmol L^{-1}, creatinine 67 µmol L^{-1}, urea nitrogen 5.8 mmol L^{-1}, bicarbonate 33.4 mmol L^{-1}, calcium 2.19 mmol L^{-1} and albumin 37 g L^{-1}. The presence of Cushing's syndrome was confirmed by increased excretion of urinary free cortisol and a failure of suppression of plasma cortisol by a low oral dose of dexamethasone. The basal plasma cortisol concentration and 24-hour urinary free cortisol excretion were extremely high (5450 nmol L^{-1} and 51460 nmol $24h^{-1}$ respectively; normal values 220-650 nmol L^{-1} and <300 nmol $24h^{-1}$). Plasma ACTH concentration was 315 ng L^{-1} (normal: <55 ng L^{-1}) and did not increase after intravenous administration of CRH. These findings, together with an insufficient fall of plasma cortisol upon continuous intravenous administration of high dose dexamethasone (1 mg h^{-1} for 7 h) , suggested an ectopic ACTH syndrome. The X-ray of the chest on the third hospital day showed effacement of the left pleural sinus and a normal heart size. A CT scan of the chest and upper abdomen disclosed bilateral pleural effusion with compression of basal lung fields, a nodular lesion of a few mm in diameter in the right upper lobe and bilateral enlarged adrenals with a picture consistent with adrenocortical hyperplasia. Viral cultures taken from the penile ulcers and ulcer on the right index finger were positive for *Herpes simplex type 2*. Serologic tests for syphilis and human immunodeficiency virus type 1 and 2 were negative. During the endocrinological work-up, the patient was given potassium suppletion, spironolactone and insulin.

On the ninth day ketoconazole (200 mg b.i.d) was started to decrease cortisol levels and treat oral thrush. The patient's condition changed dramatically on the thirteenth day with increasing dyspnoea and a fall in blood pressure. He was transferred to the ICU, intubated, artificially ventilated and treated with plasma expanders and vasoactive drugs. Blood cultures drawn on the day of his tranfer were positive for *Staphylococcus aureus*, which was also cultured from the lesion on the right index finger. A newly developed infiltrate of the left lung was seen on a repeated chest X-ray made before intubation. Upon examination of fluid obtained by bronchoalveolar washing, which was done after intubation on the day of patients transfer to the ICU, *Pneumocystis carinii* cysts were found and culture showed growth of *Aspergillus fumigatus*. A peripheral lymphocyte profile was obtained showing a depletion of both CD4 ($100x10^6$ L^{-1}) and CD8-positive lymphocytes ($40x10^6$ L^{-1}) with a normal CD4/CD8 ratio (2.4). The patient was treated with iv flucloxacilline, sulfamethoxazole/trimethoprim, amphotericine-B and because systemic herpes infection was also considered likely with iv aciclovir. The daily dose of ketaconazole was increased to 1200 mg during the following days which resulted in a rapid decrease in plasma cortisol concentrations (Fig. 1). Pulmonary status worsened however, and severe adult respiratory distress syndrome developed. Glucocorticoids were administered in the form of hydrocortisone and prednisolone. The patient died on the twenty-second day. A post mortem examination was not permitted.

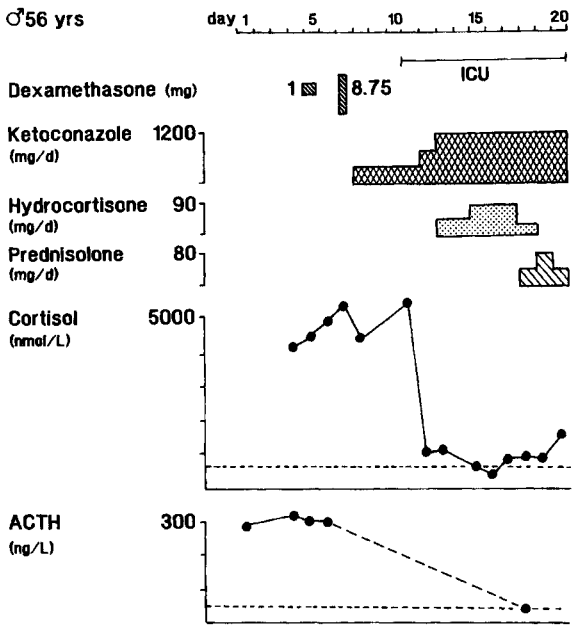

Fig. 1 - *The time course of plasma cortisol and ACTH. The patient died on the 22nd day after admission. Horizontal stippled lines indicate upper normal limits.*

DISCUSSION

The patient in this report suffered from Cushing's syndrome caused by excessive ACTH secretion. The rapid onset, the markedly elevated ACTH-

concentration, the extreme cortisol excess, and the results of the dynamic testing strongly suggested an ectopic origin of ACTH (37-39). The source might well have been a small-cell carcinoma or carcinoid tumor of the lung, representing the nodular lesion on CT scan. A remarkable feature in the clinical course was the occurrence of simultaneous infections with bacterial, viral, and fungal pathogens, which, to our knowledge, has not been reported before in patients with endogenous Cushing's syndrome. In our patient *Staphylococcus aureus* septicaemia developed from a secondary infected herpetic ulcer of the right index finger. Opportunistic pulmonary infections with *Pneumocystis carinii* and *Aspergillus fumigatus* and a multifocal skin infection with *Herpes simplex type 2* were diagnosed. A remarkable low peripheral CD4 count was observed. Unfortunately a post mortem permit was denied preventing documentation of the exact sites and extent of the infections, and the source of excess ACTH.

Opportunistic infections are well known complications of glucocorticoid therapy, but they are considered rare in patients suffering from endogenous Cushing's syndrome. Over a forty year period only 36 patients have been reported (6-36). The cause of Cushing's syndrome and diagnosed infectious agents of these patients are summarized in Table 1. Ectopic ACTH production was the predominant cause of Cushing's syndrome and diagnosed significantly more often (15/32) than in a large group of consecutive patients with Cushing's syndrome (6/121), described earlier by Biemond et al (37). From the reports on Cushing's syndrome and opportunistic infections a plasma morning cortisol concentration could be traced by us in 25 patients; it exceeded 1000 nmol L^{-1} in 19 (76%). Such high plasma cortisol concentrations are rarely seen in patients with pituitary dependent Cushing's syndrome (38-39). Four patients suffered from infections with multiple opportunistic pathogens. Twentyone of the 33 patients with known final outcome died as a result of the infection(s). The patients who died had significantly higher plasma cortisol concentrations than the ones who survived (2914±1380 *vs* 1749±1438 nmol L^{-1}; $p<0.05$). The same is true for the patients with multiple opportunistic infections (15, 21, 29) compared to those with a single infection (3755±1136 *vs* 2123±1423 nmol L^{-1}; $p<0.05$; present patient included). Fungi were the most common isolated opportunistic agents (29/41); infections with *Aspergillus fumigatus* (9), *Pneumocystis carinii* (9) and *Cryptococcus neoformans* (8) predominated. The patients with *Pneumocystis carinii* infection displayed very high plasma cortisol concentrations (not below 2759 nmol L^{-1}). In 4 of them coexisting infections with other opportunistic pathogens were present.

Table 1 - *Cause of Cushing's syndrome and infectious agents in reported cases of endogenous Cushing's syndrome complicated by opportunistic infections [6-36].*

Cause of Cushing's syndrome	number of patients
ACTH-dependent	
ectopic	15
pituitary	8
unknown	3
total	26
ACTH-independent	
adrenal carcinoma	3
adrenal adenoma	1
bilateral nodular adrenal hyperplasia	1
adrenal tumor, not specified	1
total	6
Unknown	4
Infectious agents	
Aspergillus*	9
Pneumocystis carinii	9
Cryptococcus neoformans	8
Nocardia asteroides	8
Listeria monocytogenes	2
Candida albicans	1
Candida tropicalis	1
Pseudallescheria Boydii	1
Cytomegalovirus	1
M. Tuberculosis (miliary)	1

*Aspergillus=Aspergillus fumigatus in 4 cases, non-specified in 5 cases

In the case reports with a chronologically well described clinical course, it was noticeable that the symptoms of *Pneumocystis carinii* infection invariably commenced after cortisol-lowering therapy was started. This was also true for our patient. The explanation for this paradox probably lies in the fact that strong glucocorticoid action suppresses the inflammatory response to pneumocystis infection (39-42). Of the patients mentioned in Table 1 at least seven also suffered from bacterial infections with common pathogens, which in four might have contributed to the fatal outcome.

Our review of the literature reveals that opportunistic infections in endogenous Cushing's syndrome are predominantly observed in patients with severe cortisol excess, explaining the preponderance of the ectopic ACTH syndrome in these patients.

The higher the cortisol excess, the greater the number of opportunistic infections and mortality rate. We conclude that endogenous Cushing's syndrome with a very high plasma cortisol level causes a severe immunocompromised state. Referral to a specialised endocrinological centre and prompt treatment of the hypercortisolism and concomitant infectious disease is recommended. Primary prophylaxis for *Pneumocystis carinii* infection should be considered when plasma cortisol concentrations exceed 2500 nmol L^{-1}. A high index of suspicion for (opportunistic) infections is required.

REFERENCES

1. Cushing H.
   The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism).
   Bull. Johns Hopkins Hosp. *50:* 137, 1932.
2. Brunner W.
   Pathogenese der Pancreatitis und Infectionsresistenz bei der Cushingschen Krankheit.
   Deutsche Zsch. Chir. *249:* 188, 1938.
3. Heinbecker P.
   Pathogenesis of Cushing's syndrome.
   Medicine *23:* 225, 1944.
4. Plotz C.M., Knowlton A.I., Ragan C.
   The natural history of Cushing's syndrome.
   Am. J. Med. *13:* 597, 1952.
5. Orth D.N., Liddle G.W.
   Results of treatment in 108 patients with Cushing's syndrome.
   N. Engl. J. Med. *285:* 243, 1971.
6. Weed L.A., Andersen H.A., Good C.A., Baggenstoss A.H.
   Nocardiosis. Clinical, bacteriologic and pathological Aspects.
   N. Engl. J. Med. *253:* 1137, 1955.
7. Danowski T.S., Cooper W.M., Braude A.
   Cushing's syndrome in conjunction with Nocardia asteroides infection.
   Metabolism *11:* 265, 1962.
8. Price W.F., Farmer T.A.
   Cushing's syndrome and adrenal medullary insufficiency with bilateral adrenal calcification.
   J. Clin. Endocrinol. Metab. *29:* 268, 1969.
9. Salas M., Angulo O.
   Un caso de carcinoma de la suprarrenal y pneumonia por Pneumocystis carinii.
   Gac. Med. Mex. *101:* 93, 1971.
10. Britton S., Thorén M., Sjøberg H.E.
    The immunological hazard of Cushing's syndrome.
    Br. Med. J. *4:* 678, 1975.
11. Furguson R.P., Kelly Smith J.
    Cryptococcosis and Cushing's syndrome.
    Ann. Intern. Med. *87:* 65, 1977.
12. Smith J.M., Hampton J.R., Webb R.W.
    Disseminated aspergillosis, Cushing's syndrome, and oat cell carcinoma of the lung.
    Chest *76:* 112, 1979.
13. Anthony L.B., Anthony Greco F.
    Pneumocystis carinii pneumonia: a complication of Cushing's syndrome.
    Ann. Intern. Med. *94:* 488, 1981.
14. Mossler J.A., Woodard B.H., Tannenbaum S.I., McPherson H.T., McCarty K.S. Jr.
    Cryptococcal meningitis in a patient with a functioning adrenal cortical carcinoma.
    Arch. Pathol. Lab. Med. *105:* 276, 1981.
15. Natale R.B., Yagoda A., Brown A., Singer C., Stover D., Bajorunas D.
    Combined Pneumocystis carinii and Nocardia asteroides pneumonitis in a patient with an ACTH-producing carcinoid.
    Cancer *47:* 2933, 1981.
16. Walsh T.J., Mendelsohn G.
    Invasive aspergillosis complicating Cushing's syndrome.
    Arch. Intern. Med. *141:* 1227, 1981.
17. Petersen D.P., Wong L.B.
    Nocardia infection of the hand.
    J. Hand Surg. *6:* 502, 1981.
18. Higgins T.L., Calabrese D.O., Sheeler L.R.
    Opportunistic infections in patients with ectopic ACTH-secreting tumors.
    Cleve. Clin. Q. *49:* 43, 1982.
19. Nakamura M., Kojita H., Hida T., Urabe K., Kikuchi H.
    Case of Aspergillus pneumonia associated with pituitary Cushing's syndrome.
    Horumon To Rinsho *31:* 351, 1983.
20. Kramer M., Corrado M.L., Bacci V., Carter A.C., Landesman S.H.
    Pulmonary Cryptococcosis and Cushing's syndrome.
    Arch. Intern. Med. *143:* 2179, 1983.
21. Fulkerson W.J., Newman J.H.
    Endogenous Cushing's syndrome complicated by Pneumocystis carinii pneumonia.
    Am. Rev. Respir. Dis. *129:* 188, 1984.
22. Graham B.S., Stuart Tucker W.
    Opportunistic infections in endogenous Cushing's syndrome.
    Ann. Intern. Med. *101:* 334, 1984.
23. Anonymous.
    A case of pulmonary cryptococcosis complicating Cushing's disease.
    Nippon Kyobu Shikkan Gakkai Zasshi *24:* 292, 1986.
24. Findling J.W., Buggy B.P., Segerson Th., Raff H.
    Pneumocystis carinii pneumonia complicating intermittent Cushing's syndrome.
    Wis. Med. J. *85:* 23, 1986.
25. Ansari R.A., Hindson D.A., Stevens D.L., Kloss J.G.

Pseudallescheria boydii arthritis and osteomyelitis in a patient with Cushing's disease.
South. Med. J. *80:* 90, 1980.

26. Murry P.M., Ahern M.J.
Disseminated Aspergillosis and Cushing's syndrome in a community hospital.
Conn. Med. *51:* 84, 1987.
27. Estopinan V., Cobos M.A., Hurtado A., de la Calle H.
Meningitis por Listeria monocytogenes: una rara complicación del síndrome de Cushing.
Med. Clin. (Barc.) *893:* 573, 1987.
28. Naylor C.D., Shkrum M.J., Edmonds M.W., Cholod E.J.M.
Pulmonary Aspergillosis and endopthalmitis: complications of Cushing's syndrome.
Can. Med. Assoc. J. *138:* 719, 1988.
29. Sieber S.C., Dandurand R., Gelfman N., Iannini P., Braza F.
Three opportunistic infections associated with ectopic corticotropin syndrome.
Arch. Intern. Med. *149:* 2589, 1989.
30. Tanaka M., Sato Y., Ito H., Ichikawa Y., Oizumi K., Shigemori M.
A case of Cushing's syndrome associated with Nocardia cerebral abscess.
Kansenshogaku Zasshi *65:* 243, 1991.
31. McQuillen D.P., Schroy P.C., Hesketh P.J., Sugar A.M.
Pneumocystis carinii pneumonia complicating somatostatin therapy of Cushing's syndrome in a patient with metastatic pancreatic islet cell-carcinoma and Zollinger-Ellison syndrome.
Am. J. Gastroenterol. *86:* 512, 1991.
32. Raju A.Z., Mathai D., Singh J.P., Kaur A., George S., Pulimood B.M.
Candidal oesophagitis in Cushing's syndrome.
J. Assoc. Physicians India *39:* 719, 1991.
33. Shimizu S., Yoshihara R., Ohnishi M., Ohbayashi Y., Sya S., Matsuda Y.
A case of miliary tuberculosis accompanied with adult respiratory distress syndrome (ARDS) in a patient with Cushing's syndrome.
Kansenshogaku Zasshi *66:* 93, 1992.
34. Findlay J.C., Arafah B.M., Silverman P., Aron D.C.
Cushing's syndrome with cranial and pulmonary lesions: necessity for tissue diagnosis.
South. Med. J. *85:* 204, 1992.
35. Russi E., Speich R., Hess Th., Meili E., Walter E.
Pneumocystis carinii pneumonia after transsphenoidal removal of microadenoma causing Cushing's syndrome.
Lancet *341:* 1348, 1993.
36. Boscaro M., Fallo F., Sonino N.
Disseminated nocardiosis in a patient with Cushing's syndrome.
J. Endocrinol. Invest. *17:* 443-45, 1994.
37. Biemond P., de Jong F.H., Lamberts W.J.
Continuous dexamethasone infusion for seven hours in patients with Cushing syndrome.
Ann. Intern. Med *112:* 738, 1990.
38. Howlett T.A., Drury P.L., Perry L., Doniach I., Rees L.H., Besser G.M.
Diagnosis and management of ACTH-dependent Cushing's syndrome: comparison of the features in ectopic and pituitary ACTH production.
Clin. Endocrinol. (Oxf.) *24:* 699, 1986.
39. Blunt S.B., Sandler L.M., Burrin J.M., Joplin G.F.
An evaluation of the distinction of ectopic and pituitary ACTH dependent Cushing's syndrome by clinical features, biochemical tests and radiological findings.
Q. J. Med. *283:* 1113, 1990.
40. Walzer P.D., Powell R.D. Jr, Yoneda K., Rutledge M.E., Milder J.E.
Growth characteristics and pathogenesis of experimental pneumocystis carinii pneumonia.
Infect. Immun. *27:* 928, 1980.
41. Frenkel J.K., Good J.T., Schultz J.A.
Latent pneumocystis infection in rats, relapse, and chemotherapy.
Lab. Invest. *15:* 1559, 1966.
42. The National Institutes of Health-University of California Expert Panel for Corticosteroids as Adjunctive Therapy for Pneumocystis carinii pneumonia: Consensus statement on the use of corticosteroids as adjunctive therapy for Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome.
N. Engl. J. Med. *323:* 1500, 1990.