Cytomegalovirus infection in a patient with endogenous Cushing's syndrome

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Opportunistic infections are well described complications in patients with acquired immunodeficiency syndrome, hematopoietic and lymphoreticular malignancies and Cushing's syndrome. The common infections in Cushing's syndrome are mycobacterial, fungal, bacterial and rarely viral.[1-3] However, patients with exogenous Cushing's syndrome are more predisposed to opportunistic infections than patients with endogenous Cushing's syndrome due to higher levels of circulating glucocorticoids and consequent immunosuppression. During the past decades, there have been several reports of opportunistic infections in endogenous Cushing's syndrome. Graham et al[3] in 1983 reported 23 cases of rare/unusual opportunistic infections in association with endogenous Cushing's syndrome. Subsequently, many other reports described opportunistic infections in these patients. Cytomegalovirus (CMV) infection, though a common opportunistic infection in other immunocompromised states, is very rare in endogenous Cushing's syndrome. To the best of our knowledge, only one case of CMV infection has been so far reported with endogenous Cushing's syndrome in the form of CMV pneumonitis.[4] We describe CMV colitis in a patient with endogenous Cushing's syndrome.

A 27-year-old man was admitted with history of rapid weight gain, striae, proximal muscle weakness and increasing pigmentation for the last 2 years. He had no history of exogenous steroid intake. On examination, his body mass index (BMI) was 33 Kg/m^2, and had purple striae, proximal muscle weakness and pulp atrophy. His blood pressure was 190/110 mm Hg and had features of psychosis. Biochemistry showed serum sodium 135 meq/L, potassium 2.1 meq/L, blood glucose 21.8 mmol/L, serum cortisol at 8 am 880 nmol/L, at 10 pm >1200 nmol/L, and 10 pm adrenocorticotropic hormone (ACTH) 137 pg/ml. Serum cortisol levels following overnight dexamethasone challenge was 440 nmol/L while low dose challenge was 600 nmol/L and high dose challenge was 540 nmol/L. A computed tomography (CT) scan of the chest showed mediastinal lipomatosis and CT of adrenals revealed bilaterally enlarged adrenal glands. An MRI of the pituitary was non-contributory. Meta-iodo-benzyl gauanidine (MIBG) scan to look for any nueroendocrine tumor did not reveal any abnormality. He was treated with spironolactone, amlodipine, potassium supplementation, insulin and ketoconazole 800 mg in divided doses to control hypertension and metabolic derangement due to hypercortisolemic state.

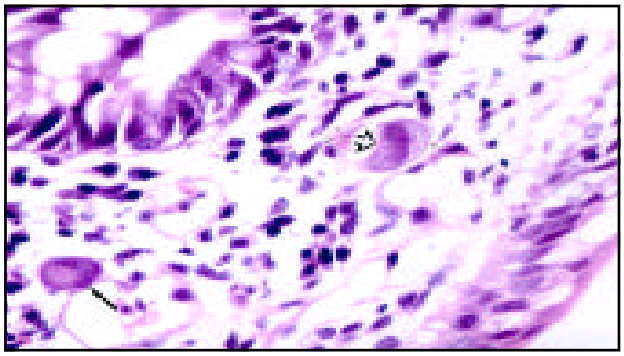

Figure 1 - High power photomicrograph of colon showing cytomegalovirus inclusion bodies in capillary endothelial cells (arrow) and the macrophage in laminapropria (open arrow) (Hematoxylin and eosin x 550).

During his hospital stay he had bloody diarrhea. Stool examination did not reveal any cysts/ova and amoebic serology titre was insignificant. Colonoscopy was performed, which revealed multiple ulcerations in the sigmoid and transverse colon. Biopsy from these lesions showed cytomegaly and cytomegalovirus inclusion bodies (**Figure 1**) Both CMV pp65 and anti CMV immunoglobulin IgM were negative. An HIV serology was non-reactive. He was put on ganciclovir for 4 weeks and ketoconazole was continued. With this treatment, the bloody diarrhea subsided and serum cortisol decreased to 600 nmol/L at 8 am and 700 nmol/L at 4 pm. Repeat colonoscopic biopsy was performed after 4 weeks, which revealed evidence of chronic colitis without any viral inclusion bodies or cytomegaly. He was subsequently subjected to bilateral adrenalectomy as no definite source of ACTH could be localized with available investigations. The paired adrenals weighed 36 gm (N<12 gm) and histopathology showed bilateral hyperplastic glands. He was discharged on replacement doses of prednisolone and fluorohydrocortisone, and is doing well on follow-up. Repeat colonoscopy performed after 3 months was normal.

Glucocorticoids have long been known to alter the host response to infectious processes. Harvey Cushing[5] observed that "glucocorticoids excess appears to leave the patient with a definite susceptibility to infections". Patients with endogenous Cushing's syndrome are predisposed for fungal infections (*Cryptococcosis*, *Aspergillosis)*, non opportunistic bacterial infections (*Staphylococcus*, *Listeria*, *Nocardia*), or reactivation of tuberculosis. However, reports of opportunistic infection in them are rare. Amongst the endogenous

Cushing's, a higher risk of infection related complications occur in ectopic ACTH syndrome and contributed to 91% in one series.[3]

Cytomegalovirus is an extremely rare cause of opportunistic infection in patients with endogenous Cushing's syndrome, occurring in severely immunocompromised patients. Previously, a lone case of CMV pneumonitis had been reported in endogenous Cushing's syndrome with multiple opportunistic infections, including disseminated *Aspergillosis* and *Pneumocystis carinii*.[4] Cytomegalovirus colitis is one of the important manifestations of the viral involvement of the gastrointestinal tract. It usually presents with pain abdomen and bloody diarrhea due to thrombosis of small arterioles and infarction of the bowel. This is more commonly observed in immunosuppressed individuals with reported prevalence varies from 2-16% in solid organ transplant recipients, and 38% in bone marrow transplant recipients.[6] Presentation with blood mixed stool, demonstration of CMV inclusion bodies in colonic mucosal cells, response to ganciclovir with repeat normal colonic biopsy substantiate the diagnosis of CMV colitis in our patient.

The effect of glucocorticoids on leukocyte function is more profound than on cellular immunity, with humoral immunity being the least affected. Altered antigen presentation by macrophages to lymphocytes, lymphocyte apoptosis, suppression of local inflammatory mediators like interleukins -1 and -6 (IL-1, IL-6), tumor necrosis factors, interferons, prostaglandins and leukotrienes may be important in the pathogenesis of opportunistic infections. The various factors which determine the risk of infection are severity and duration of glucocorticoids excess, metabolic clearance, coincident immunosuppression and host factors.[1-2]

In conclusion, it is difficult to predict the type of microorganism in a patient with endogenous Cushing's syndrome as these patients are predisposed to infections by unusual pathogens. Therefore, an aggressive approach with emphasis on tissue diagnosis and normalization of hypercortisolemic state is rewarding.

Received 6th December 2004. Accepted for publication in final form 13th April 2005.

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References

1. Hart PD, Russel E, Remington JS. The compromised host and infection. ***J infect Dis*** 1969; 120: 169-191.
2. Aucott JN. Glucocorticoids and infection. ***Endocr Metab Clin North Am*** 1994; 23: 655-670.
3. Graham BS, Tucher WS. Opportunistic infections in endogenous Cushing's syndrome. ***Ann Intern Med*** 1984; 101: 334-338.
4. Sieber SC, Dandurand R, Gelfman N, Iannini P, Braza F. Three opportunistic infections associated with ectopic corticotropin syndrome. ***Arch Intern Med*** 1989; 149: 2589-2591.
5. Cushing H. The basophil adenomas of pituitary body and their clinical manifestations (pituitary basophilism). ***Bull Johns Hopkins Hosp*** 1932; 50: 137-195.
6. Buckner FS, Pomeroy C. Cytomegalovirus disease of the gastrointestinal tract in patients without AIDS. ***Clin Inf Dis*** 1993; 17: 644-656.