IDCases 27 (2022) e01420

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Case report

Multiple concomitant life-threatening opportunistic infections due to uncontrolled hypercortisolism

Sarah Al Qassimi[a,*], Ahmad Nusair[b], Mohamad Mooty[b], Adnan Ajmal[c], Saaid Abdel-Ghani[a]

[a] Medical Subspecialties Institute – Hospital Medicine, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
[b] Medical Subspecialties Institute – Infectious Diseases, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
[c] Medical Subspecialties Institute – Endocrinology, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates

ARTICLE INFO

Article history:
Received 29 November 2021
Received in revised form 21 January 2022
Accepted 22 January 2022

Keywords:
Cushing's syndrome
Hypercortisolism
Opportunistic infections
Disseminated aspergillosis
Cytomegalovirus endophthalmitis
Pneumocystis Jirovecii pneumonia

ABSTRACT

Opportunistic infections associated with severe cortisol excess carry a high mortality rate and are most prevalent with ectopic ACTH syndrome. There are limited reports of these cases described in the literature. In this case report, we describe multiple severe life-threatening opportunistic infections due to endogenous hypercortisolism. Our patient, against numerous expectations, survived multiple opportunistic infections including disseminated invasive aspergillosis, *Cytomegalovirus* endophthalmitis and *Pneumocystis Jirovecii* pneumonia, reinforcing the need for multidisciplinary care for patients presenting with complicated hypercortisolism.

Introduction

Cushing's syndrome is an endocrine disorder featuring excessive levels of cortisol. Opportunistic infections are known to occur in patients with hypercortisolism [7]. There are case reports of opportunistic infections due to endogenous hypercortisolism however, the majority reported monomicrobial opportunistic infections [5]. There are only two case reports of mortality due to polymicrobial infections in patients with endogenous hypercortisolism found in the literature (Bakker, 1998; Song, 2020). In the following case report, we aimed to highlight the management of a complicated case of polymicrobial infection in the setting of hypercortisolism.

Case report

A 23-year-old Somali male was admitted to an outside facility for a 3-week history of fatigue and polyuria. He was diagnosed with diabetes mellitus and discharged on oral hypoglycemic agents but returned to the hospital and found to have worsening hyperglycemia, hypertension and severe hypokalemia. He was evaluated for hypercortisolism with a battery of tests including an adrenocorticotropic hormone (ACTH) level of 54 pmol/L, an overnight 1 mg dexamethasone test that showed failure of cortisol suppression (AM cortisol: 1583 nmol/L), an elevated 24-hour urine cortisol (> 11380 nmol/day) and an MRI brain that revealed a 1-cm focal lesion involving the right pituitary gland concerning for a microadenoma. He was subsequently referred to our facility for neurosurgical evaluation the following week.

On arrival, the patient had elevated blood pressure with a cushingoid appearance, moon facies, scattered hyperpigmented macules and nonpigmented abdominal striae. Endocrinology confirmed the diagnosis of ACTH-dependent Cushing syndrome and recommended additional work up for a possible ectopic ACTH source due to his severe presentation. Our work up included random cortisol of 2684 nmol/L, ACTH of 47.45 pmol/L and 24-hour urine free cortisol of > 12691 nmol/d. We conducted 8 mg dexamethasone overnight suppression test with AM cortisol of 2806 nmol/L, which was suggestive of an ectopic source of ACTH rather than the pituitary. AM cortisol from the day of dexamethasone administration was 2219 nmol/L, showing no more than 50% decrease in cortisol. Visual field testing was normal and DEXA scan showed low bone mass of spine with Z score of − 2.6.

Chest computerized tomography (CT) scan was done on admission and, compared with the CT scan from the referring facility the week prior, showed rapid progression of a left upper lobe consolidation with surrounding ground glass opacification that favored a necrotizing lobar pneumonia with parapneumonic effusion and a healing anteromedial right second rib fracture was noted. An

* Corresponding author.
E-mail address: sarahalque@gmail.com (S.A. Qassimi).

https://doi.org/10.1016/j.idcr.2022.e01420
2214-2509/

abdomen/pelvis CT scan revealed bulky adrenal glands consistent with ACTH-dependent Cushing's syndrome and hypodensities suspicious of paraganglioma, which was later rule out by normal plasma fractionated metanephrines and catecholamines.

He was initiated on empiric amoxicillin/clavulanic acid for suspected community acquired pneumonia, which was later changed to piperacillin-tazobactam and azithromycin by Infectious Diseases (ID) team owing to his immunocompromised state. ID recommended bacterial, fungal and mycobacterial sputum cultures, diagnostic bronchoscopy, HIV screen and fungal serologies. Within a week, repeat CT scan of the chest showed progressive disease burden with development of cavitary lesions prompting an empiric change in antimicrobial coverage with meropenem and voriconazole and further workup with a diagnostic bronchoscopy.

During the same time period, from Endocrine's standpoint, corticotropin-releasing hormone (CRH) stimulating test and the 8 mg dexamethasone suppression test were done, which was consistent with ectopic Cushing's. In light of equivocal results from biochemical testing, the source of hypercortisolism was still unclear so the consensus was to proceed with inferior petrosal sinus sampling (IPSS) in conjunction with Interventional Radiology.

Two weeks after admission to our facility, he began to have worsening back pain, lumbar and thoracic CT scans were performed, revealing radiographic evidence of multiple new thoracic and lumbar vertebral compression fractures.

In view of this continual worsening, he was transferred to the intensive care unit (ICU) for etomidate infusion to induce adrenal suppression. In the interim, his aspergillus galactomannan and beta-D glucan assays were elevated, 2.68 index and > 500 pg/mL respectively. Antifungal therapy was optimized by adding caspofungin for suspected invasive pulmonary aspergillosis. It was decided that he should have at least one week of adrenal suppression and aspergillosis therapy prior to IPSS. This was when his pending bacterial and fungal cultures also resulted positive for aspergillus species.

Subsequently he started to complain of blurred vision a few days after his transfer to the ICU. MRI brain revealed multifocal cavitating ring-enhancing lesions dispersed throughout the brain suggestive of hematogenous dissemination of possible fungal/mycobacterial infection. In light of this finding, IPSS was deemed to bear high risk of further dissemination. He was now considered a case of disseminated invasive aspergillosis with central nervous system involvement and his antifungal therapy plan was shifted from caspofungin to liposomal amphotericin along with voriconazole. Fundoscopic ophthalmic examination was compatible with right sided endogenous endophthalmitis, raising possibility of fungal or viral etiologies. He was found to be viremic for CMV (27,900 IU/mL) and thus valganciclovir was started along with viterous voriconazole installation. BAL stain were positive for *Pneumocystis jivorecii* (PCJ) and IV trimethoprim-sulfamethaxazole was added for superimposed PCJ pneumonia. The case was rediscussed with Neurosurgery, Endocrinology and Infectious Diseases with the unanimous decision to proceed with transsphenoidal resection of pituitary adenoma, which resulted in immediate remission of hypercortisolism. Post-operative MRI brain revealed gross total resection that was negative for complications.

His subsequent ICU course was complicated by new-onset large left-sided hydro-pneumothorax with worsening cavitation of the left lung noted three weeks after his transfer to the ICU. A chest tube was placed with good improvement. He was tracheostomized electively soon afterwards. He was treated for several additional infections afterwards including *Clostridioides difficile* infection, *Pseudomonas aeruginosa* pneumonia and ESBL *E. coli* urinary tract infection.

He was stepped down to the acute care unit after approximately a month in the ICU, where he was continued on medical management and in-patient rehabilitation prior to being discharged 2 weeks later to a long-term healthcare facility. His hypercortisolism continues to stay in remission. He was to continue on voriconazole for 9 months-1 year, TMP-SMX for chronic prophylaxis and replacement therapy including hydrocortisone, levothyroxine and vitamin D.

Discussion

Our case is distinctive in terms of the combination of disseminated invasive aspergillosis, *Cytomegalovirus* endophthalmitis and *Pneumocystis jivoreci* pneumonia that has not been reported in the past. Although there have been three case reports describing multiple infections due to severe hypercortisolism in the literature, two of the patients did not survive the overwhelming complications of their infections [11,2,3]. Pleiotropic effects of cortisol are the main drivers of opportunistic infections in immunosuppressed patients, as virtually every cell in the immune and inflammatory response of the body is affected [7]. Notably, patients with endogenous Cushing's syndrome and those taking exogenous corticosteroids are susceptible to the same spectrum of opportunistic infections [6].

In a case series by Graham, it was found that the most common life-threatening opportunistic infections in hypercortisolism include *Pneumocystis jirovecii, Cryptococcus neoformans, Aspergillus fumigatus* and *Nocardia asteroides*. In the same study, they suggested that not only does the degree of hypercortisolism increases the risk for opportunistic infections but specific cortisol thresholds can potentially predict what type of infection the patient could acquire [5]. Generally, it holds true that the higher the level of cortisol, the greater the burden of opportunistic infections [2]. The progression of any infection in patients with hypercortisolism is blunted and tend to run a silent course, further delaying diagnosis [10]. The first description of disseminated aspergillus infection in patients with hypercortisolism was reported in 1981, wherein autopsy findings were suggestive of disseminated aspergillosis in the central nervous system, lungs, heart, kidneys and pleurae [12]. Another recent case report described a patient who presented with disseminated invasive aspergillosis in the setting of a cortisol-producing adrenocortical carcinoma [4]. Our patient had a rapidly progressing process with minimal signs and symptoms of infection that was seemingly unresponsive to broad-spectrum antibiotics, which is how invasive fungal infections often present. Although aspergillus endophthalmitis has been described in one case report in the literature [8], our case is the first reported example of *Cytomegalovirus* endophthalmitis occurring in the setting of hypercortisolism. As previously mentioned, *Pneumocystis jirovecii* is one of the most common infectious complications of hypercortisolism. PJP is a well established complication of steroid therapy in immunocompromised patients with the first case of PJP as a complication of endogenous hypercortisolism being described in 1981 [1]. In light of this, PJP prophylaxis in hypercortisolism with trimethoprim-sulfamethoxazole is available, especially for patients with a urine free cortisol > 5-fold normal [9].

In conclusion, our case confirmed that a multidisciplinary approach to complicated uncontrolled hypercortisolism is warranted. Suspicion and screening of opportunistic infections in uncontrolled hypercortisolism should be done and acted upon without delay in conjunction with suppressing cortisol production to prevent further life-threatening deterioration. Figs. 1–8.

Ethics approval and consent to participate

No ethical approval needed for case report.

Financial Support

No funding bodies contributed to this work.

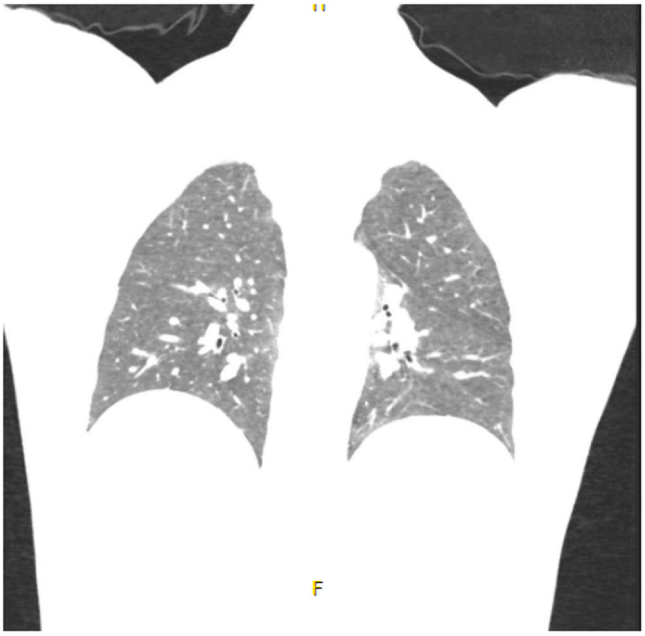

Fig. 1. Baseline normal CT Chest on 11/2020 from the referring hospital.

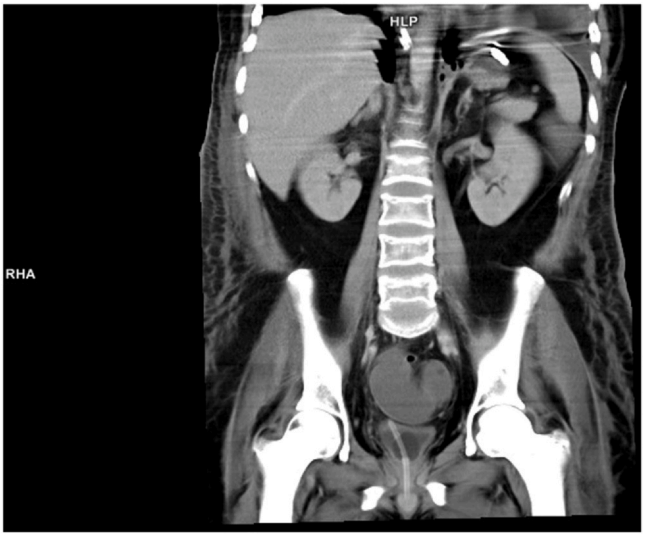

Fig. 2. CT Abdomen/Pelvis on 1/12/2020 showing 2 morphologically normal adrenal glands.

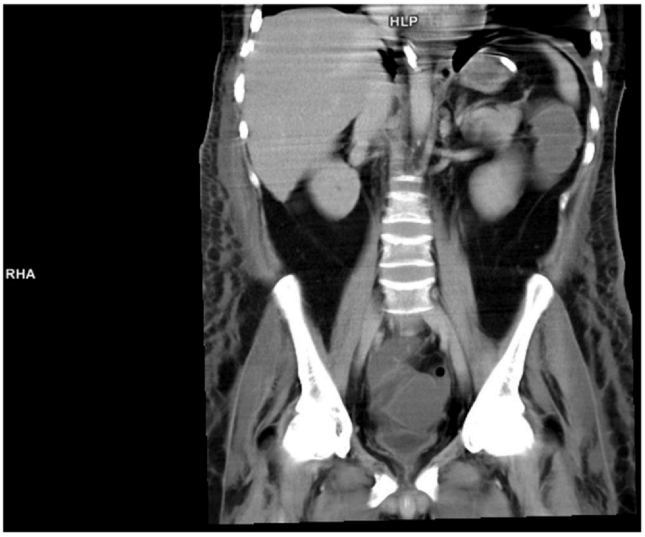

Fig. 3. CT Abdomen/Pelvis on 1/12/2020 shows the para-adrenal lesion medial to the left gland and lateral to the lumbar spine.

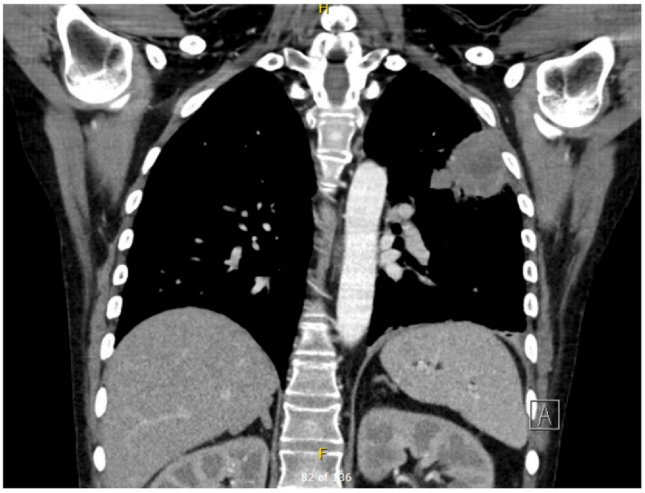

Fig. 4. CT Chest on 1/12/2020 showing left pulmonary consolidation.

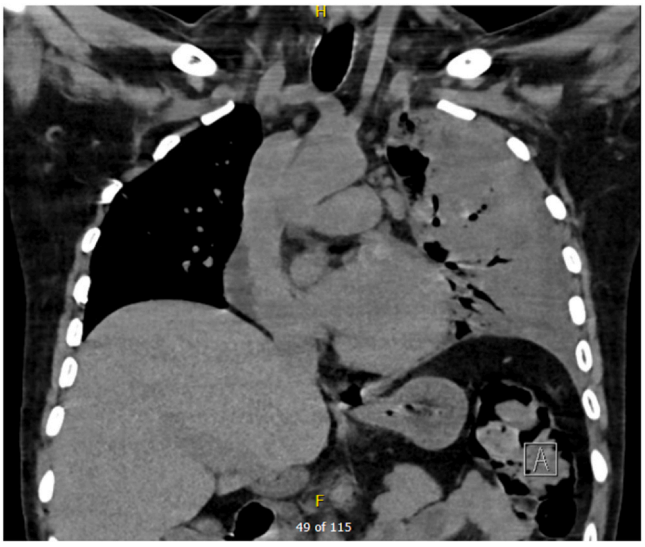

Fig. 5. CT Chest on 10/12/2020 showing progressive extension of left sided consolidation with progressive pleural effusion and a cavitating left upper lobe mass.

CRediT authorship contribution statement

Sarah Al Qassimi: Writing – original draft. **Ahmad Nusair**: Writing – review & editing. **Mohamad Mooty**: Writing – review & editing. **Adnan Ajmal**: Writing – review & editing. **Saaid Abdel-Ghani**: Writing – review & editing.

Declaration of Competing Interest

No competing interest to declare from all authors.

Acknowledgement

None.

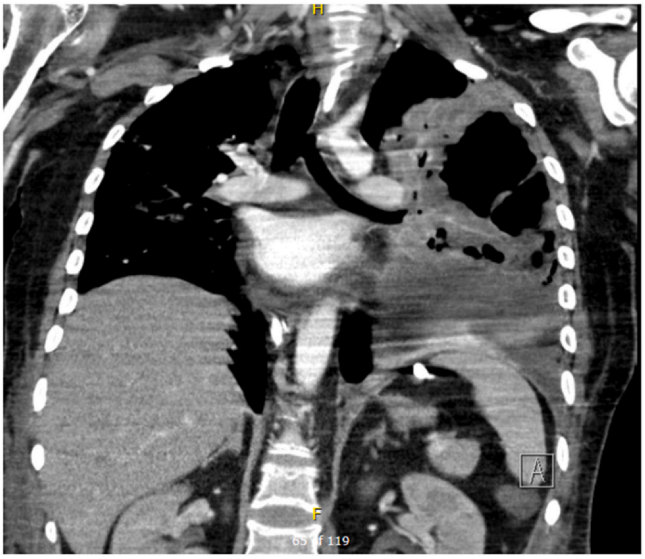

Fig. 6. CT Chest on 29/12/2020 showing significant increase in size of a fungal cavitary pneumonia mainly occupying the left upper lobe containing multiple air-fluid levels.

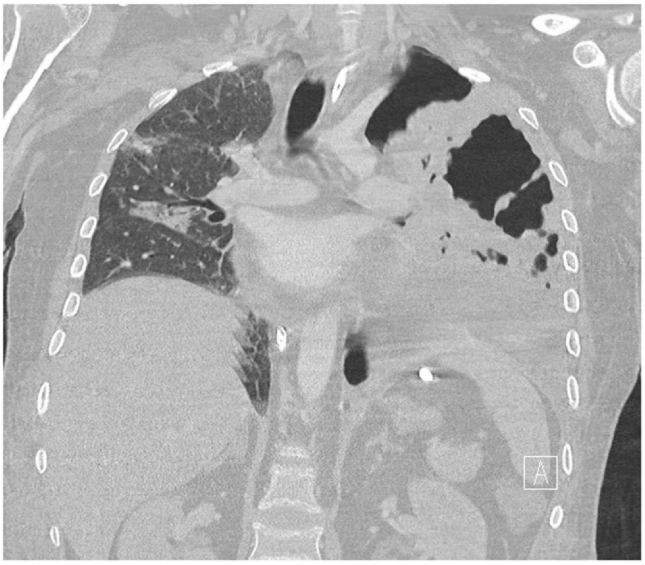

Fig. 7. Accompanying CT Chest image on 29/12/2020 showing significant increase in size of a fungal cavitary pneumonia mainly occupying the left upper lobe containing multiple air-fluid levels.

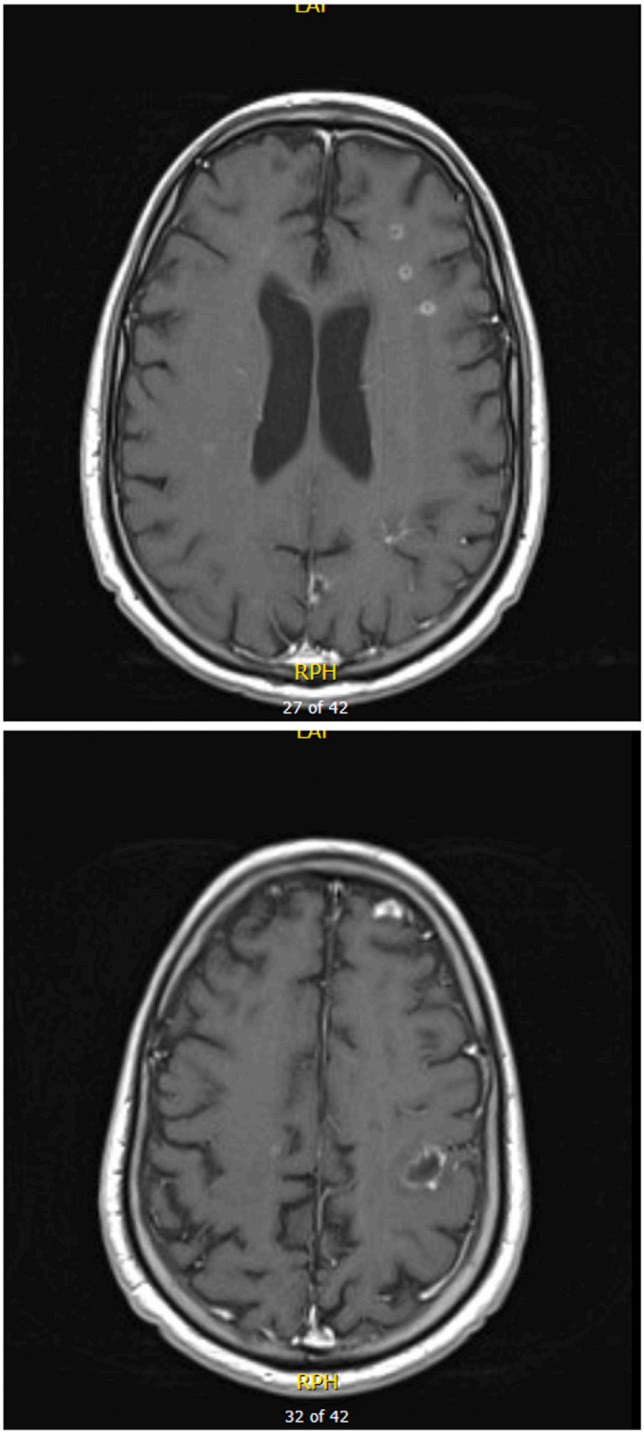

Fig. 8. MRI Brain on 11/12 revealing multiple multifocal cavitating ring-enhancing lesions dispersed throughout the brain.

References

[1] Anthony LB. Pneumocystis carinii Pneumonia: a complication of cushing's syndrome. Ann Intern Med 1981;94(4_Part_1):488–9. https://doi.org/10.7326/0003-4819-94-4-488

[2] Bakker RC, Gallas PRJ, Romijn JA, Wiersinga WM. Cushing's syndrome complicated by multiple opportunistic infections. J Endocrinol Investig 1998;21(5):329–33. https://doi.org/10.1007/BF03350337

[3] Chan C, Roberts JM. Ectopic ACTH syndrome complicated by multiple opportunistic infections treated with percutaneous ablation of the adrenal glands. Case Rep 2017;2017:bcr. https://doi.org/10.1136/bcr-2017-221580

[4] Chen Cardenas SM, Colovic K, Nicol TL, Maleki Z, Krug E. Disseminated invasive aspergillosis in a patient with adrenocortical carcinoma. AACE Clin Case Rep 2019;5(4):e233–7. https://doi.org/10.4158/ACCR-2019-0016

[5] Graham BS. Opportunistic infections in endogenous cushing's syndrome. Ann Intern Med 1984;101(3):334–8. https://doi.org/10.7326/0003-4819-101-3-334

[6] Kansagara DL, Tetrault J, Hamill C, Moore C, Olson B. Fatal factitious cushing's syndrome and invasive aspergillosis: case report and review of literature. Endocr Pract 2006;12(6):651–5. https://doi.org/10.4158/EP.12.6.651

[7] Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. Lancet 2003;362(9398):1828–38. https://doi.org/10.1016/S0140-6736(03)14904-5

[8] Naylor, C.D., Phil, D., Shkrum, M.J., Edmonds, M.W., & Cholod, E.J.M., 1988, Pulmonary aspergillosis and endophthalmitis: Complications of Cushing's syndrome. 2.

[9] Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, Savage MO, et al. Treatment of Cushing's syndrome: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2015;100(8):2807–31. https://doi.org/10.1210/jc.2015-1818

[10] Sarlis, N.J., Chanock, S.J., & Nieman, L.K., 2000, Cortisolemic Indices Predict Severe Infections in Cushing Syndrome Due to Ectopic Production of Adrenocorticotropin. 85(1), 6.

[11] Song BG, Lim MG, Bae JH, Hong JH, Lee SG, Park SH, et al. Multiple opportunistic infections related to hypercortisolemia due to adrenocortical carcinoma: a case report. Infect Chemother 2020;53:797–801. https://doi.org/10.3947/ic.2020.0205

[12] Walsh, T.J., & Mendelsohn, G., 1981, Invasive Aspergillosis Complicating Cushing's Syndrome. 2.