Candida albicans endophthalmitis in a patient with a non-functioning pituitary adenoma evolving into Cushing's disease: A case report

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ABSTRACT

A 53-year-old woman presented with complaints of blurred vision in the left eye. She had been treated for recurrent non-functioning pituitary adenoma (NFPA). A vitreous biopsy followed by histopathologic examination showed the presence of Candida albicans. Meanwhile, Cushing's disease was diagnosed and gamma knife surgery was performed. Vitrectomy and antifungal treatment improved ocular infection and inflammation. Herein, we describe the first case of C. albicans endophthalmitis in a patient with NFPA evolving into Cushing's disease.

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1. Introduction

Candida endophthalmitis is a potentially sight-threatening ocular condition. Candida albicans exists as a benign commensal organism in the gastrointestinal (GI) tract and mucous membranes of healthy individuals but causes infections in susceptible individuals [1]. Hematogenous spread of the microorganism from an infected site into the eye may cause endogenous endophthalmitis. Predisposing risk factors, such as intravenous drug abuse, immunodeficiency, prolonged systemic corticosteroid or antibiotic therapy, cytotoxic chemotherapy, and long-term parenteral feeds, increase the likelihood of infection [2].

There have been few reports of a non-functioning pituitary tumor evolving to Cushing’s disease [3,4]. A clinical manifestation of those patients appears to be different from those who presented with Cushing’s disease at onset and from those who had persistent silent corticotroph pituitary adenomas. They do not show clinical features of hypercortisolism at onset, but eventually evolved to a full-blown Cushing’s disease that cause hypercortisolemia and variable clinical manifestations. Glucocorticoids exert many complex quantitative and qualitative immunosuppressive effects that induce cellular immunodeficiency, which increases host susceptibility to opportunistic infections. Herein, we report a rare case of C. albicans endophthalmitis in a patient with a clinically non-functioning pituitary adenoma evolving into Cushing’s disease.

2. Case

A 53-year-old Korean woman presented with a 2-month history of blurred vision and floaters in her left eye. She had a medical history of recurrent non-functioning pituitary adenomas. She had got the transsphenoidal surgeries in 2005 and 2008, and then craniootomy in 2009 in other hospital. She visited a neuro-surgeon in our hospital due to recurred pituitary tumor and got the third transsphenoidal surgery in 2011. On April 2012, the pituitary tumor was recurred again, and we treated her with gamma-knife surgery (GKS). Her serum adrenocorticotropic hormone (ACTH) and cortisol levels were 38 pg/ml (normal, 0–60 pg/ml) and 10.5 μg/dL (normal, 5–25 μg/dL), respectively. She showed no clinical feature of Cushing’s syndrome and the overnight dexamethasone suppression test was not done in our hospital at this point. Histologic diagnosis was consistent with a non-secreting pituitary adenoma with positive staining only for ACTH.

On November 2013, this patient had been admitted to the otorhinolaryngology service with severe otalgia, vertigo, tinnitus, and associated cutaneous vesicular eruption around the right ear for 2 weeks. A diagnosis of herpes zoster oticus (HZO) was made.
and she had received intravenous acyclovir, dexamethasone, and ceftriaxone. Dexamethasone was administered intravenously for 6 days and then switched to oral prednisone for 6 days. During this admission, ACTH levels were 892 pg/mL and cortisol levels were 119 μg/dL as a regular check-up for pituitary adenoma. She also had been newly diagnosed with diabetes mellitus during the admission. Hemoglobin A1c was 6.5%, but plasma postprandial glucose level was over 300 mg/dL. Therefore, we started glimepiride and metformin. Her ear symptoms improved after one week of hospitalization and she was discharged.

At 20 days after discontinuation of steroid, we repeated plasma ACTH and serum cortisol level. Plasma ACTH (684.3 pg/mL) and cortisol (59.2 μg/dL) levels were still high. Then, the patient presented with headache and blurred vision in the left eye, and was referred to us for ophthalmological review on 30 December 2013 (day 0).

On baseline examination, best corrected visual acuities were 20/20 in the right eye and 20/1000 in the left. Intraocular pressure was 12 mmHg in the right eye and 11 mmHg in the left. Slit-lamp examination showed mild (1 +) inflammatory reaction in the anterior chamber and anterior vitreous in her left eye. Ophthalmoscopy of the left eye revealed vitreous haze along with large, fluffy, creamy white epiretinal mass and retinal infiltrates near the foveal center (Fig. 1a). Fundus fluorescein angiography showed blocked fluorescence due to vitreous haze and fluffy epiretinal mass, leakage of dye from the optic disc, and capillary leakage in the temporal retina (Fig. 1b). Optical coherence tomography (OCT) scan confirmed the presence of overlying fluffy balls extending into the vitreous body (Fig. 1c and d). Findings from the right eye were nonspecific except for mild diabetic retinopathy with a few microaneurysms. Based on the clinical features, a diagnosis of endogenous fungal endophthalmitis of the left eye was made.

Polymerase chain reaction analysis of aqueous humor was negative for cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and varicella-zoster virus. The patient promptly underwent diagnostic and therapeutic vitrectomy (day 7). During the vitrectomy, multiple infiltrates in the deep retina with overlying vitreous fluffy balls were noted. The vitreous samples, including the vitreous fluffy balls, were obtained at the onset of vitrectomy and were sent for microbiological testing. From this sample, immunohistochemical staining revealed filamentous fungus with elongated pseudohyphae (Fig. 2) and culture yielded positive growth for *C. albicans* using standard microbiological techniques. Final biochemical organism identification for *C. albicans* was performed by VITEK 2 automated system (bioMérieux, Marcy l’Etoile, France). Following confirmation of fungus by direct microscopy, intravenous fluconazole 400 mg once daily and prophylactic oral bactrim 480 mg once daily treatments were immediately commenced since 6 January 2014 (day 7). Blood and urinary cultures were negative and the serology for human immunodeficiency virus was negative. There was no evidence of other systemic involvement.

![Fig. 1. Pre-operative clinical photographs. A Fundus photographs of the patient’s left eye showing a fluffy white epiretinal mass (white arrows) and vitreous infiltrates (white arrowheads) at initial presentation. B Fluorescein angiography showing blocked fluorescence due to vitreous haze and fluffy mass. Leakage of dye from the optic disc and capillary bed in the temporal retina (white arrowheads) is also observed. C, D Horizontal (C) and vertical (D) 6-mm scans centered on the foveal pit on swept-source optical coherence tomography (OCT) demonstrates large fluffy balls extending into the vitreous body (white arrows) and dense vitritis (white arrowheads). Long thin white arrows indicate OCT scan direction.](image-url)
Meanwhile, Cushing’s syndrome was diagnosed with a 646 µg/day of 24-h urine free cortisol and a 114 µg/dL of serum cortisol level after high-dose dexamethasone suppression test (day 3). Furthermore, brain magnetic resonance imaging (MRI) revealed a 1-cm contrast-enhancing sellar mass indicative of tumor recurrence (Fig. 3). Corticotrophin releasing hormone (CRH) test and Octreo-scan were not available at the time of diagnosis and inferior petrosal sinus sampling could not be performed in fear of the spread of candida endophthalmitis. Pituitary carcinoma was also suspected based on its aggressive behavior, but there was no evidence of intracranial or systemic metastasis on whole body positron emission tomography/computed tomography (PET/CT). The tumor was hard to remove because it abutted right cavernous internal carotid artery, and responded well to the previous GKS. Thus, the patient underwent GKS at two days after the vitrectomy (day 9). Concomitantly, cortisol lowering therapy with oral mitotane and cabergoline was commenced.

Her eye symptoms improved following the vitrectomy and systemic antifungal therapy. She was discharged from the hospital on 11 January 2014 (day 12) after 6 days of intravenous fluconazole therapy. After discharge, she was treated as an outpatient with fluconazole (oral, 400 mg daily) for 2 weeks from 12 January (day 13) to 28 January 2014 (day 29). Two months after discharge (day 73), her vision had improved slightly to 20/500 with macular depigmented changes (Fig. 4a). There was a complete resolution of retinal infiltrate. However, the visual outcome was poor due to foveal thinning and photoreceptor disruption (Fig. 4b and c). Hypercortisolism was resolved 3 months after GKS followed by cortisol lowering therapy. On the last visit on 26 May 2014 (day 147), her ACTH level...
dropped to 132.4 μg/mL. Her serum cortisol was 9.4 μg/dL and 24-h urine free cortisol was 13.8 μg/day.

3. Discussion

C. albicans is the most common cause of endogenous fungal endophthalmitis [5]. Candida endophthalmitis mostly presents as unilateral posterior uveitis associated with fluffy white vitreous and retinal infiltrates. Vitreous opacities, sometimes connected by strands of inflammatory material that have often been described as a ‘string of pearls’ appearance, may be noted. This infection almost always occurs in patients who are immunocompromised or have other predisposing risk factors [2]. Although our patient had a very typical Fundus appearance suggestive of fungal endophthalmitis, it was very unusual in that she had a clinically non-functioning pituitary adenoma evolving into Cushing’s disease which shows a high degree of hypercortisolism later on.

This patient presented a curious clinical profile that strongly suggests the metamorphosis from a non-functioning to an ACTH-producing pituitary adenoma. Secondary occurrence of florid Cushing’s disease from a previous silent or non-functioning pituitary adenoma has been described in the previous several reports [3,4,6]. Metamorphosis of silent pituitary adenoma to Cushing’s disease is considered to be a distinct disease entity. The progression mechanisms of this type of tumor have not yet been completely elucidated. However, some hypotheses have been proposed as an impaired proopiomelanocortin processing leading to insufficient production of ACTH, and too low percentage of immunoreactive ACTH-secreting cells. Another possible mechanism is the increased intracellular degradation of ACTH, not allowing clinical expression of its production. If there is a decrease in this cellular degradation during tumor progression, ACTH synthesis may become clinically significant.

Prolonged exposure to glucocorticoids impairs immunity and predisposes the patient to various viral, bacterial, fungal, and parasitic infections [7]. This vulnerability is attributed to the complex immunity dysregulation caused by glucocorticoids. Especially, glucocorticoids have long been recognized as a risk factor for candidal infection [8]. Heidenreich et al. [9] reported that glucocorticoids affect the capacity of monocytes to control extra-cellular growth of Candida species by inhibiting tumor necrosis factor-α secretion. Furthermore, studies in mice have shown that glucocorticoids increase both C. albicans burden in the GI tract and, indirectly, the frequency of C. albicans translocation from the GI tract to the bloodstream [10,11]. What is significant, however, is that the extent of immunologic impairment and the risk of opportunistic infections correlates with the degree of hypercortisolism [12]. Therefore, those with higher levels of cortisol due to adrenal tumors or ectopic ACTH syndrome are more likely to have an opportunistic infection than those with pituitary Cushing’s disease [12,13]. In addition, those receiving exogenous glucocorticoid therapy are at much more risk of developing opportunistic infections than those with endogenous Cushing’s syndrome [12].

There are several reports describing invasive candidiasis such as esophagitis [14], endocarditis [15], and disseminated disease [13,16] in patients with endogenous Cushing’s syndrome. In addition, there are several reported cases of ocular candidiasis in exogenous Cushing’s syndrome [17,18]. However, in the literature, to our knowledge, there has been no previous case report of confirmed ocular candidiasis in patients with an endogenous Cushing’s syndrome, especially a clinically non-functioning pituitary adenoma evolving into Cushing’s disease.

In this case, the patient had several systemic risk factors for developing fungal endophthalmitis in addition to an endogenous Cushing’s syndrome: use of broad-spectrum ceftriaxone, systemic steroid for the treatment of HZO, diabetes mellitus, and acute illness with hospitalization. Although it is unknown which predisposing factor contributed most to the development of fungal endophthalmitis, we speculate that the exposure to high endogenous cortisol levels was mostly associated with the development of opportunistic infections, such as HZO and C. albicans endophthalmitis, because first onset of ocular symptoms correlated with the time when her plasma ACTH and cortisol levels were markedly elevated. The patient complained the blurred vision before she had been treated with steroid and her glycemic level was well-controlled. Therefore, we assumed endogenous hypercortisolism contributed to the development of opportunistic infections in this patient rather than systemic steroid or diabetes mellitus.

Pars plana vitrectomy can be used in patients with fungal endophthalmitis. Advantages of this technique are thought to be a reduction of infectious load, an increase in intraocular diffusion of systemically administered antifungal medication, and a reduction in the risk of retinal detachment by limiting vitreoretinal traction [19,20]. In fact, higher levels of endogenous hypercortisolism contribute to the subclinical manifestations of infections because of its anti-inflammatory properties and make it difficult to diagnosis. Therefore, cultures of vitreous specimens obtained by prompt vitrectomy should be considered for detecting the causal organism in fungal endophthalmitis with endogenous hypercortisolism. In addition, the probability of an unrecognized infection should be always considered, even if there was no evidence of fungemia or bacteremia.

In our case, the ocular inflammatory activity such as vitritis and retinal infiltrates subsided after vitrectomy and systemic antifungal therapy. However, despite infection and inflammation control, preoperative foveal photoreceptor damage resulted in poor visual outcome. This is consistent with the poor visual prognosis associated with C. albicans endophthalmitis, particularly in patients with poor presenting visual acuity or centrally located lesion, reported by Sallam et al. [2]. This also implies that the need for early diagnosis should be stressed to provide specific therapy before sequelae develop.

In summary, this interesting case illustrates that C. albicans endophthalmitis can occur in patients with an endogenous Cushing’s syndrome. When the clinical findings, such as indolent chronic posterior uveitis with accompanying vitritis, are present in patients with an endogenous Cushing’s syndrome, fungal endophthalmitis must be suspected. This is especially true for those who develop florid Cushing’s syndrome from years of silence. Diagnostic and therapeutic vitrectomy should be considered for confirming a definitive diagnosis and it may facilitate a favorable response with prompt systemic antifungal treatment.

Conflict of interest

No competing interests. Not submitted for publication elsewhere.

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