Case Report

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Effect of clarithromycin in von Hippel-Lindau syndrome: a case report

Xin Ma, Yuanyuan Jing, Yan Liu and Lisheng Yu

Abstract

Von Hippel-Lindau (VHL) syndrome is caused by germline mutations in the *VHL* gene and is accompanied by the development of both benign and malignant tumors. Clarithromycin (CAM) is a widely used anti-inflammatory drug that has also been proven effective for treating some cancers. In this study, we present a novel case of a 38-year-old female patient with VHL syndrome confirmed by computed tomography, with no relevant family history. The patient was only offered close follow-up observation after diagnosis, but was orally administered CAM twice daily when her disease progressed. After treatment for 3 months, her inner ear tumors had stopped growing and her kidney cysts had shrunk. Her pancreatic tumors treated with CAM showed no significant increase in size, and the lymph node swelling disappeared. CAM treatment was interrupted for 2 years and then stopped for 5 years when improvements were noted; the patient's condition thereafter gradually improved and finally stabilized with no obvious side effects. We discuss this case in the context of the published literature and consider the possible mechanisms of CAM action in the treatment of VHL syndrome. To our knowledge, this is the first case report of a patient with VHL syndrome treated with CAM.

Keywords

Clarithromycin, von Hippel-Lindau syndrome, genetic disease, central nervous system hemangioblastoma, renal cell carcinoma, pancreatic tumor

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Introduction

Von Hippel-Lindau (VHL) syndrome is a rare hereditary tumor syndrome that manifests with various neoplasms in individuals with *VHL* gene mutations.[1] Patients with

Department of Otolaryngology, People's Hospital of Peking University, Beijing, China

Corresponding author:
Lisheng Yu, Department of Otolaryngology, People's Hospital of Peking University, 11 South Xizhimen Street, Xicheng District, Beijing 100044, China.
Email: listentoyu@163.com

VHL syndrome generally develop both benign and malignant tumors, including lesions of the central nervous system (CNS) and visceral lesions, such as cerebellar hemangioblastomas, retinal angiomas, pancreatic cysts, renal tumors, and epididymal adenomas.[2] Patients may also suffer from related pheochromocytomas. The clinical spectrum of tumors varies widely among affected families. VHL syndrome can be subdivided into two subtypes, VHL type 1 and VHL type 2. Patients with VHL type 1 usually develop hemangioblastomas and renal clear cell carcinomas, but not pheochromocytomas, whereas VHL type 2 patients frequently develop pheochromocytomas.[3] Among the multiple tumors caused by VHL syndrome, renal cell carcinoma (RCC) is the most prevalent tumor, and the leading cause of death in VHL patients. VHL syndrome is associated with high mortality and disability; however, there is currently no effective method for reversing the *VHL* mutation, and no satisfactory treatment for this disorder.

Clarithromycin (CAM) is a new type of 14-ring macrolide antibiotic commonly used in the clinic as an anti-inflammatory drug.[4] Evidence has revealed that CAM may also preserve body weight and physical independence, and prolong survival in patients with lung cancer,[5,6] possibly associated with its anti-inflammatory effect.[7–9] CAM has also been shown to suppress corneal neovascularization by reducing vascular endothelial growth factor (VEGF) expression,[10] thus demonstrating a role in the regulation of angiogenesis and implying a potential anti-angiogenic effect in addition to its known anti-inflammatory function.[11] For instance, CAM has demonstrated a positive role in the treatment of some hematological cancers via its immunomodulatory and anti-cancer effects.[12–14] We therefore speculated that CAM might be an effective treatment in patients with VHL syndrome.

In this study, we present the novel case of a 38-year-old female patient with VHL syndrome who experienced significant improvement after CAM administration. We also discuss this case in the context of the published literature, and consider the possible mechanism of CAM action in the treatment of VHL syndrome.

Case report

We report on a 38-year-old female patient who provided consent for publication of this case report. She was routinely admitted for a check-up on 26 May 2007. A pancreatic abnormality was detected via B-mode ultrasonography. The patient's history revealed a transitory experience of seeing objects in shades of grey as far back as 1987. She became dizzy when tired or underwent mental stress and preferred to rest in a dark place if possible. The patient had a syncopal attack lasting for 2 to 3 minutes in an elevator in May 1996 and had experienced persistent episodes of vertigo or syncope and tinnitus since the age of 18 years. She developed gradual hypoacusis in her left ear in 2003 and experienced her most recent episode of syncope in June 2003, when she was totally deaf in her left ear. Furthermore, two renal cysts approximately 1×2 cm were discovered in 2003, though the precise details were unknown. A mucus cyst was found in her right ovary in May 2005 and she underwent surgical removal of the right ovary by laparoscopy on 8 August 2005. The patient was married when she was 26 years old, and had a healthy daughter in 2005. The patient's father and aunt had no history of Meniere's syndrome.

B-mode ultrasound conducted on 29 May 2007 revealed a pancreatic polycyst with partial consolidation, suggestive of a mucinous cystadenoma or cystadenoma. The possibility that it was partly malignant or bleeding could not be excluded.

A retroperitoneal polycyst was considered as a disseminated polycystic kidney. The patient was generally in good condition and no abnormalities were found in the lung, abdomen, thyroid, blood, urine, and feces. Tumor markers including CEA, CA199, CA72.4, CA242, and CA125 were all within normal ranges, except for CA153 which was slightly elevated. Gastrin norepinephrine, epinephrine, and dopamine were all within normal levels. Head computed tomography (CT) and fundus examination showed no abnormalities. Abdominal and pelvic CT scans on 30 May 2007 revealed a pancreatic polycyst-occupying lesion below the front head of the pancreas, which was considered to be a cyst-solitary papilloma; occupying lesions below the back of the pancreas head, which were considered to be islet cell tumors; polycysts in both kidneys with an occupying lesion in the inferior pole of the right kidney, which was identified as a hematoma or RCC; and a node in the left adrenal, which was judged as an adenoma. Recurrence of a cystadenoma in the bilateral adnexal nodes was not excluded. A comprehensive analysis of the above pathological changes indicated a likely diagnosis of VHL syndrome. A chest CT performed on 6 June 2007 showed multiple lymphoid knots in the mediastinum, suggesting the need for a re-examination; the twelfth thoracic vertebra presented with high-definition sub-nodes, suggesting the need for a bone scan. Cephalic CT and magnetic resonance imaging carried out on 4 June 2007 revealed no abnormalities. A fundus examination performed on 8 June 2007 showed no abnormality of the papilla of the optic nerve or retina in either eye.

Nucleotide changes in the resected tumor tissues indicated heterozygosity of the *VHL* gene at 451A>T (Figure 1), and an amino acid change from ATC → TTC at 151I → F. Investigation of the human gene mutation database confirmed that this was a novel mutation. These findings supported a diagnosis of VHL syndrome. There is currently no effective therapy for VHL syndrome apart from surgical interventions. Multi-site surgery is difficult in patients with systemic multiple tumors, and close follow-up observation is therefore the only practical option. However, during observation of the current patient, her kidney, pancreas, and inner ear tumors gradually increased in size, with the kidney tumors exceeding 3 cm, suggesting that they were malignant. The patient was therefore started on oral administration of CAM at 250 mg twice daily, supplemented with BIFICO to protect the gastrointestinal mucosa. In March 2008, on compassionate grounds, written informed consent and confirmation of eligibility were obtained from the patient.

CT and MRI were performed during CAM treatment to monitor changes in the tumors in the abdomen and inner ear. Postoperative follow-up CT after 3 months showed that the inner ear tumors had stopped growing and the kidney cysts had shrunk. Further basic maintenance of the pancreatic tumors, including treatment with CAM and regular monitoring, showed no significant increases. The patient underwent several subsequent reviews, which showed little change in pancreas size (Table 1). A review on 13 February 2009 showed that the pancreatic tumor, cystic renal lesions, and solid nodules were all significantly diminished in both size and number. The nodules at the lower pole of the right kidney were reduced compared with the previous examination; their last estimated size was approximately 1.6×1.9 cm, and this remained unchanged for 4 further years, with no new solid components. A renal cortex lesion measuring 1.8×1.6 cm in the central area was narrower than before (Table 1). Annual examinations thereafter revealed that pancreas and kidney functions were within normal

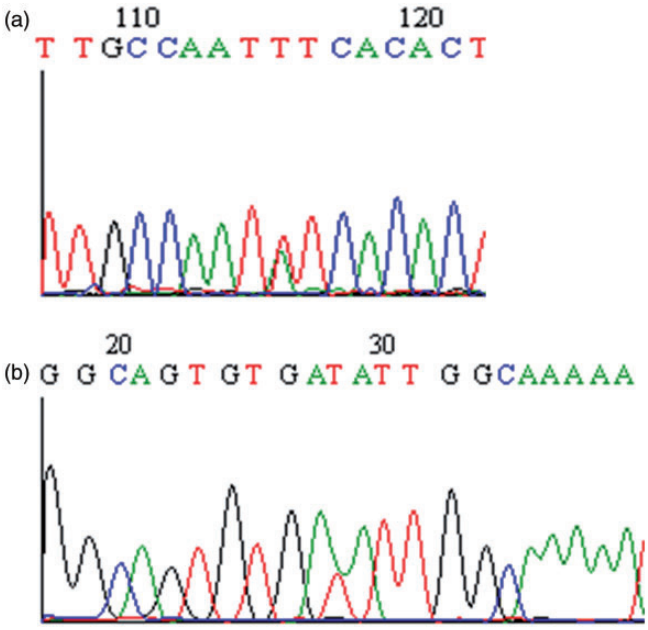

Figure 1. Genetic testing of the patient with VHL and the normal person. a: Sequence change in forward primer region of the patient with VHL and the normal person. b: Sequence change in reverse primer region of the patient with VHL and the normal person.

Table 1. Changes in lesions after treatment with clarithromycin.

Date	Lesion in head of pancreas (cm)	Lesion in posterosuperior pancreas (cm)	Cystic degeneration in upper pole of right kidney (cm)	Nodule in inferior pole of kidney (cm)	Bilateral Adnexa (cm)	Endolymphatic Sac (cm)
2007-5-30	4.5 × 3.7 × 3.4	2.6 × 1.9	2.6 × 2.0	2.6 × 2.4	2.6 × 2.0 3.0 × 2.0	
2008-6-30	4.0 × 4.3 × 3.7	2.6 × 1.9	unchanged	1.9 × 1.8	3.7 × 2.4 4.5 × 2.4	
2009-2-13	4.3 × 3.7 × 4.0	unchanged	5.3 × 4.8	1.91.6		
2009-9-3	4.3 × 4.1	2.7 × 2.0	5.2 × 5.0	1.8 × 1.6		
2009-11-19	4.7 × 4.4	2.8 × 2.1	5.7 × 5.3	1.8 × 1.6		
2010-3-9	4.8 × 4.6	2.8 × 2.1	5.9 × 5.1	1.8 × 1.6		
2010-9-10	4.8 × 4.6	2.8 × 2.1	5.9 × 5.1	1.8 × 1.6		

ranges, indicating no significant pancreas or kidney damage, and there was no subsequent sign of recurrence on CT scans. The changes in the patient's left lymph node are shown in Figure 2. No gut flora imbalances were found after drug administration. There were no adverse effects of CAM.

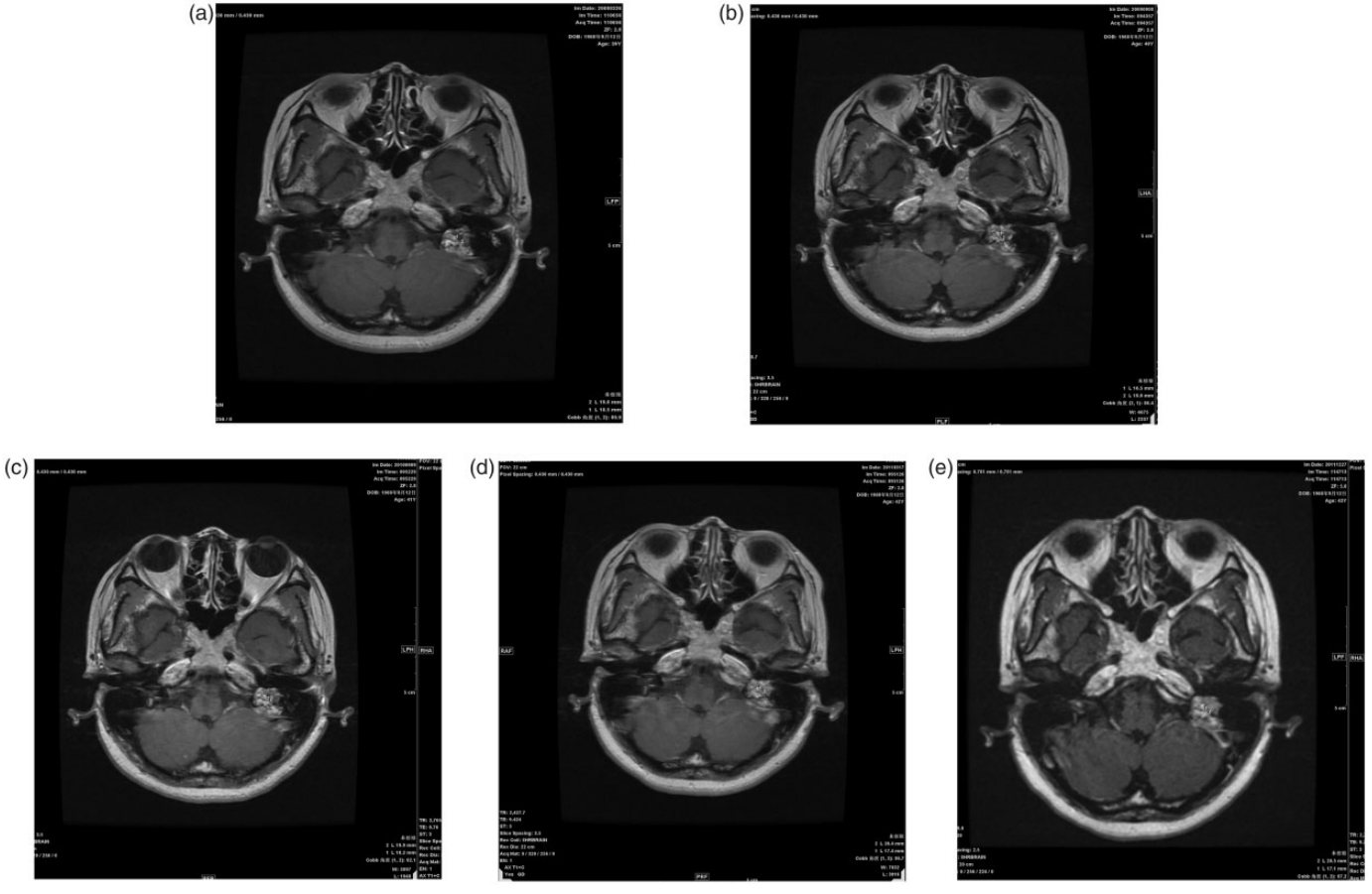

Figure 2. Computed tomography scans showing left endolymphatic sac (arrow) after treatment with clarithromycin on 26 March 2008 (a), 8 September 2009 (b), 9 September 2010 (c), 17 March 2011 (d), and 27 December 2011 (e).

Discussion

VHL syndrome was officially named by Melmon and Rosen in 1964. This syndrome is characterized by CNS hemangioblastoma accompanied by cysts of the pancreas and kidney, pheochromocytoma, renal carcinoma, and skin adenoma. Thus, VHL syndrome is identified as a genetic condition involving renal carcinoma and renal clear cell neoplasm. VHL syndrome is an autosomal dominant genetic disease with an incidence of 1/36,000.[15] One report based on 47 cases across four generations showed that VHL syndrome-related diseases mainly included retinal angioma (27.8%), CNS hemangioblastoma (50.0%), renal cysts and carcinoma (55.6%), and pancreatic cysts (38.9%). The incidence of lymph sac tumors in the general population is very low, but the morbidity in VHL patients is approximately 11%, and VHL syndrome is the only disease characterized by bilateral lymph sac malignancies.[15,16] CNS hemangioblastoma and RCC are the most common causes of VHL-associated death. Surgery is currently the main therapeutic option for VHL disease, but given the presence of the disease in multiple organs and its high recurrence rate after resection, surgical treatment is difficult and cannot remove all lesions or prevent its recurrence. There is also no specific drug for targeting VHL to date.

The current clinical diagnostic criteria for VHL syndrome include a family history of hemangioblastoma or visceral lesions, while patients without a family history are diagnosed by the presence of more than two hemangioblastomas or one hemangioblastoma accompanied by one visceral tumor.[17] A genetic diagnosis is the gold standard for VHL diagnosis. The current case was diagnosed definitively by genetic analysis, which confirmed a *VHL* gene mutation. *VHL* is a tumor suppressor gene and its loss, mutation, or deactivation by methylation may result in abnormal VHL protein synthesis, representing the molecular basis of VHL disease. VHL disease can be divided into two types based on different genetic mutations,[18] with the main difference between the two types manifesting as differences in the morbidities of RCC, hemangioblastoma, and pheochromocytoma. The genetic changes in type I VHL involve missing and truncated sequences, and it is clinically characterized by the lack of pheochromocytomas. In contrast, the genetic changes in type II VHL involve missense mutations, which are often accompanied by pheochromocytomas. Type II VHL can be further divided into subtypes A, B, and C, with a lower incidence of RCC in type IIA, higher incidences of renal carcinoma, hemangioblastoma, and pheochromocytoma in type IIB, and a high incidence of pheochromocytoma in type IIC.

Inflammation is considered to play a critical role in the multiple pathogenesis of VHL. The immune systems in individuals expressing heterozygous *VHL* genes display an increased inflammatory response, which contributes to the secretion of cytokines that can in turn promote tumor occurrence by enhancing cell proliferation. Inflammation can also induce genetic changes in precancerous cells via the oxidation of reactive oxygen species or the inactivation of mismatch repair enzymes.[19] Rudolf Virchow first proposed an association between inflammation and cancer after the discovery of white blood cells in the tumor in the 19th century, but it was not until nearly a decade afther this initial discovery that inflammation was confirmed to play a key role in tumorigenesis and some of the relevant molecular mechanisms were clarified. Clear cell renal carcinomas with *VHL* mutations have been shown to produce excessive levels of pro-inflammatory cytokines, such as tumor necrosis factor-α and transforming growth factor-β, and to

enhance the activity of nuclear transcription factor-κB.[10]

CAM is a new type of 14-ring macrolide antibiotic widely used in the clinic as an anti-inflammatory drug.[20] In addition to its anti-inflammatory effects, its biological response regulatory effects have also caused increasing interest in recent years.[21] CAM can regulate angiogenesis by affecting cytokine biology, and might thus possess potential anti-angiogenic effects. Considering these effects of CAM, we tested the hypothesis that long-term treatment with CAM may thus inhibit the expression of relevant inflammatory factors affected by *VHL* gene mutations, inhibiting angiogenesis and controlling the development of malignant tumors associated with VHL disease. In the current case, the renal tumor tended to shrink and remained stable for 5 years after administration of oral CAM, with no side effects. Notably, the renal tumor was never histologically proven to be RCC, possibly because of its benign nature, thus supporting the significance of CAM treatment in this patient with VHL syndrome.

The *VHL* gene produces the protein pVHL, which plays a critical role in regulating hypoxia pathways via the transcription factor hypoxia-inducible factor.[22] Generally, functional loss of pVHL can contribute to the stabilization of hypoxia-inducible factor-α and resultant upregulation of pro-tumorigenic molecules, including the growth factors VEGF, platelet-derived growth factor, and transforming growth factor-α.[1] These upregulated target factors subsequently cause rapid proliferation, angiogenesis, and tumorigenesis. CAM may regulate angiogenesis by affecting cytokine levels and lead to potential anti-angiogenic effects. Tumor angiogenesis is a critically controlled multi-step process regulated by a series of stimulatory and inhibitory factors that act on the existing vasculature and may be involved in the formation of new blood vessels. More than 20 angiogenic factors have been found to date, including at least 15 angiogenesis-inhibiting factors. VEGF is recognized as one of the most important angiogenesis factors, and numerous studies have suggested that VEGF is abnormally expressed in many tumors,[23–25] and can act as a reliable independent prognostic factor for tumor cell development and behavior. CAM was shown to significantly inhibit the expression of VEGF in human lung cancer cells,[26] as well as suppressing corneal neovascularization by reducing VEGF expression.[10] Based on these results, we speculated that the basis of CAM action in VHL syndrome may be associated with its ability to regulate VEGF.

The present report describes a patient with VHL syndrome who was treated with CAM. Follow-up observations suggested that her renal tumor decreased and then remained unchanged for 5 years. There were no obvious side effects of oral CAM. This case highlights the potential effectiveness of CAM for the treatment of VHL syndrome. However, large clinic trials involving more types of tumors are needed to verify the curative effect of CAM, which has the potential to become an effective therapy for VHL-associated lesions.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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