

Coexistent Non-Hodgkin's Lymphoma and Renal Cell Carcinoma in a Patient with Von Hippel-Lindau Disease: A Case Report

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Abstract

Von Hippel-Lindau (VHL) disease is an autosomal dominant syndrome that, due to loss of tumor suppressor gene function, predisposes affected individuals to various benign and malignant tumors including renal cell cancer. In contrast, lymphomas are a varied group of clonal diseases arising from a lymphocyte progenitor and can affect any site of the lymphatic system. We present the case of a 56 year old female with Von Hippel-Lindau disease and clear cell renal carcinoma (CCRC), who developed a nasopharyngeal mass with cervical and submandibular lymphadenopathy subsequently proven to be a Non Hodgkin's lymphoma (NHL). Though the association between VHL and renal cell cancer is significant, a mechanism linking these two diseases has previously been unknown. To the best of our knowledge, this is the first reported case of a patient presenting with coexistent VHL and NHL. In an effort to explain this rarity, we propose that a defective VHL allele may serve as a possible link between VHL and RCC, thus leading to an environment that would favour the development of a malignant clone, our patient's NHL.

Background

With a prevalence of 1 per 36,000 people [1], von Hippel-Lindau (VHL) disease is an autosomal dominant syndrome that, due to loss of tumor suppressor gene function, predisposes affected individuals to various benign and malignant tumors. Such tumors have historically included hemangioblastomas of the retina and central nervous system, renal cell carcinoma (RCC), pheochromocytomas, and tumors of the pancreas, middle ear, epididymis, and broad ligament [1-3]. Lymphomas, on the other hand, are a varied group of clonal diseases that arise from a lymphocyte progenitor and can affect any site of the lymphatic system [4]. Specifically, Non Hodgkin's lymphoma (NHL) is the fifth most common malignancy in American adults with 30- 40% of new cases classified as diffuse large B-cell Lymphoma (DLBCL), an aggressive subtype with the highest overall incidence [5,6]. Though the association between NHL and RCC is significant, no clear explanation for such association has been provided [7-10]. To the best of our knowledge, this is the first reported case of a patient presenting with VHL and NHL. Additionally, we provide a potential explanation for the association between NHL and RCC through the role of defective VHL product causing increased Vascular Endothelial Growth Factor Receptor (VEGF) levels ultimately leading to increased tumor angiogenesis.

Case Report

A 56 year old white female with past medical history significant for VHL disease with associated stage IV clear cell renal carcinoma (CCRC) presented to our facility in January of 2007 for further management of her CCRC. Her family history was significant for an aunt and a sister also having VHL disease. Prior to her transfer of care, she was treated in 1981 with a partial right nephrectomy. In 2002 she experienced reoccurrence of the CCRC and thus a total right nephrectomy was performed. She also previously had two cerebellar hemangioblastomas excised. Computed tomography of the chest, abdomen, and pelvis done for restaging purposes at our facility revealed a 2.5 x 1.9 cm lesion in her left lung, mediastinal lymphadenopathy, and cystic lesions in her left kidney and pancreas. A positron emission tomography scan showed abnormal uptake in the left lung and left kidney lesions with 3 areas of increased uptake in the right renal bed, all consistent with recurrence of her CCRC. Magnetic resonance imaging of the brain revealed no new

lesions. The patient was asymptomatic and accordingly opted to pursue a period of watchful waiting of her CCRC.

In August of 2007 she developed a persistent non-productive cough and noticed a 1 cm enlarged tender lymph node in her left parotid region. A course of antibiotics did not improve her symptoms. She denied any fevers, chills, fatigue, or night sweats but noticed worsening cervical lymphadenopathy and otalgia. Otolaryngoscopic exam revealed a nasopharyngeal mass. Initially a fine needle aspiration (FNA) was obtained from one of the accessible neck masses with tumor cells returning positive for CD20, proliferation marker Ki67 (M1B1), CD45, CD79a, and vimentin, and negative for CD3, CD10, pan- cytokeratin, EMA, S100, and neuroendocrine markers. These findings were consistent with DLBCL. This was further confirmed by biopsy of her nasopharyngeal mass, which showed atypical cells that were positive for CD20 and CD43 and negative for CD3, CD10, and CD30, confirming the diagnosis of DLBCL.

By this time, her exam revealed multiple areas of posterior cervical and submandibular lymphadenopathy of various sizes with the largest node measuring 3 cms. Given her profound pain secondary to the significant lymphadenopathy, she completed standard treatment with Rituximab, Cytoxan, Adriamycin, and Vincristine (R-CHOP) and central nervous system prophylaxis with intrathecal methotrexate. She tolerated the chemotherapy well and experienced both a slight decrease in the size of her pulmonary nodule and dramatic resolution of her lymphadenopathy. The left kidney remained stable with lesions consistent with her CCRC and VHL disease.

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The patient did well clinically for several months until she presented with a new right neck mass in January of 2009. A FNA of the mass was limited by the low number of cells obtained but was again consistent with a B cell neoplasm with the majority of cells returning positive for CD10, CD19, and bright monoclonal surface kappa. Concurrent imaging did show recurrence in her right axilla but no other areas were involved. The patient has declined salvage therapy and elected to return to a period of watchful waiting over both her CCRC and NHL as she is now again relatively asymptomatic. Her CCRC has had only minimal growth during this time.

Discussion

To the best of our knowledge, this is the first reported case of co-existing VHL disease and NHL. Though the metachronous occurrence of NHL following renal cell cancer has been reported in literature [8-9,11-12] the underlying factors that contribute to such an association have remained unclear. Genetic predisposition to cancer, or similarities in the immune mechanisms associated with these neoplasms have been suspected [10]. Our case, however, provides another potential explanation for this association, which may lie in our patient's underlying VHL disease.

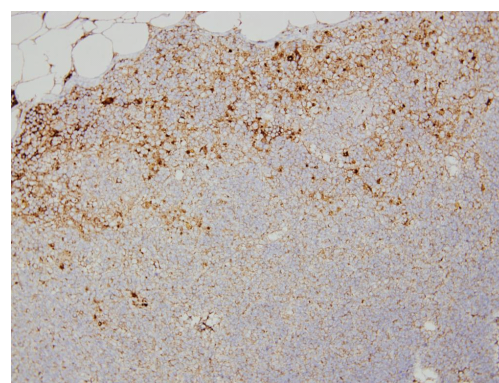
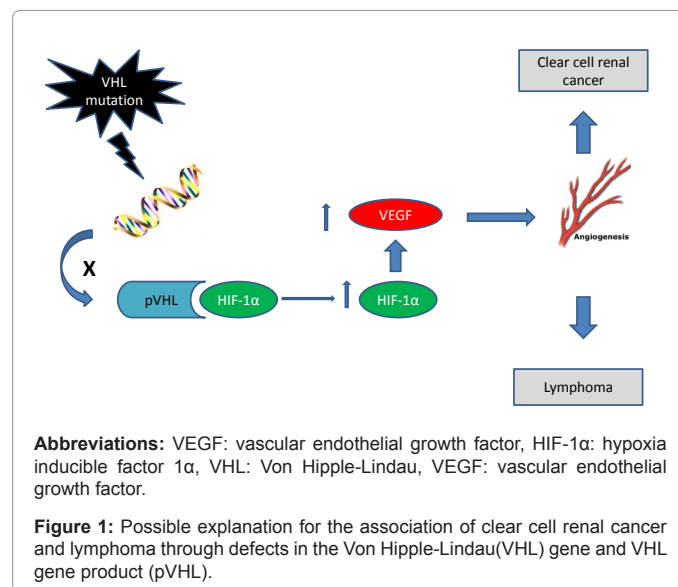
The VHL gene has been shown to produce a gene product, pVHL, which usually functions as a tumor suppressor gene. Therefore, for pVHL associated tumors to form, both a germ line mutation which inactivates one copy of the VHL gene and either a somatic mutation or deletion of the second gene copy has to occur, a process well known as the "two hit model" [13]. pVHL participates in many cellular pathways and when deleted may lead to uncontrolled growth and metabolic activity.

One instance where the role of pVHL is evident is its effect on Hypoxia Inducible Factors (HIFs), a family of transcription factors that regulate the expression of several genes involved in the body's response to hypoxia [13,14]. In normoxic environments, the α subunit of HIF-1, which is sensitive to oxygen levels, is hydroxylated and bound to pVHL. When this occurs, the unit becomes covalently linked to ubiquitin, which then marks it for degradation by proteasomes. Since the protein is degraded, there is no increase in the mRNA transcription of erythropoietin, an unnecessary process as there would already be enough oxygen via adequate blood flow to that area. However, in low oxygen environments, such as one in which rapid tumor growth is consuming large amounts of oxygen, there is no hydroxylation, HIF accumulates, and increased transcription of erythropoietin leads to increased oxygen delivery through increased red blood cell production [14].

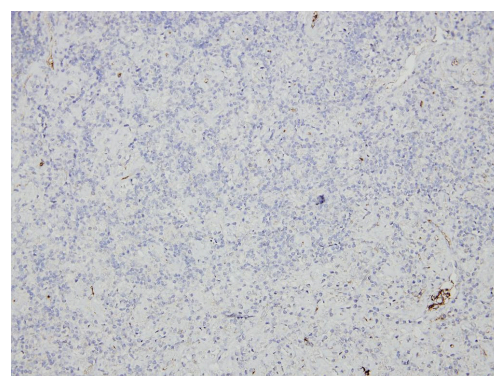
In contrast, in patients with VHL disease, the sole functioning VHL allele also becomes ineffective, causing a situation similar to hypoxia with the result being increased angiogenesis [13,15]. When cells lack pVHL, HIF accumulates and activates the transcription of several genes involved in adaptation to hypoxia. These genes include vascular endothelial growth factor (VEGF) which promotes angiogenesis, erythropoietin which promotes erythropoiesis, and platelet derived growth factor B which promotes mitogenesis [13]. Additionally, pVHL downregulates metalloproteinase like MMP1 and upregulates MMP inhibitors (TIMPs) [16]. pVHL is also associated with overproduction of carbonic anhydrases 9 and 12, which are responsible for acidification of the microenvironment [17]. Collectively, these changes result in enhancing tumor growth and invasion.

We hypothesize that our patient's absence of a functioning

pVHL in association with her VHL disease lead to upregulation of HIF, subsequent increase in VEGF gene expression, and ultimately to increased angiogenesis (Figure 1). To prove that VEGF was overexpressed, we stained our patient's lymph node biopsy for VEGF, and indeed, it showed increased expression of VEGF (Figure 2A). In comparison, a control lymph node specimen from a patient with



(A)



(B)

Figure 2: Our patient's lymph node biopsy showing increased VEGF expression (A) compared to the control biopsy from a patient with only RCC (B). Note the increased VEGF expression in A.

only RCC and no underlying VHL did not display increased VEGF expression (Figure 2B).

Furthermore, the correlation between HIF activation and VEGF receptor activation in B-cell lymphomas has been well documented in a paper published by Giatromanolaki et al. [18]. This study examined the expression of the phosphorylated and thereby activated form of VEGF receptor 2 (KDR) in patients with B-cell non-Hodgkin's lymphoma. The cytoplasmic expression of KDR was increased in 55% of patients with DLBCL. The upregulation of HIF was thought to be related to intralosomal hypoxia or an oncogenic pathway that stabilized HIF or stimulated HIF transcription [15]. Likewise, in our case, the defective pVHL may have acted to stabilize HIF, preventing its degradation by the proteasomes. Increased VEGF expression in lymphoma has led to several studies exploring anti-VEGF strategies for treatment. For example, bevacizumab (Avastin) has shown modest activity as a single agent in relapsed aggressive lymphomas [19] or in combination with chemotherapy in upfront setting [20].

On the other hand, studies have also revealed that VEGF mRNA levels are highest among patients with CCRC in comparison to other forms of RCC [15-17]. Additionally, CCRC has been associated with deletions of chromosome 3p, which in turn has been associated with pVHL inactivation [16]. These observations not only explain why VHL disease is associated with CCRC, but also provides an explanation for the increased frequency of CCRC compared to other histologies in cohorts of patients with coexisting renal tumors and lymphomas [7, 10].

Though the presence of VHL disease was not reported in the other cases of NHL in association with CCRC, we speculate the occurrence of an acquired mutation or VHL gene inactivation due to DNA hypermethylation in these cases [23]. In one series, for example, VHL mutation and loss of heterozygosity were detected in 57% and 98% of sporadic renal cell carcinoma cases, respectively [24]. Because we did not examine the lymphoma cells for loss of wild type VHL allele, we cannot establish that VHL mutation was causally linked to NHL. Accordingly, the association between CCRC and NHL in our case might be totally incidental.

Obviously, the presence of elevated VEGF levels secondary to VHL might not be the only explanation for the association of clear cell renal carcinoma and NHL. For instance, someone might argue that NHL has never been reported in association with VHL disease before. One explanation for the rarity of NHL in VHL population is related to the natural history of the disease, where the median survival of VHL disease patients is 49 years, with renal cell cancer being the leading cause of death [2]. Our 56 year old patient had an unusually indolent disease course in terms of her clear cell renal carcinoma, which may have provided a longer period of time with presumed chronically elevated VEGF levels secondary to her VHL, leading to the development of a second malignancy. Additionally, the epigenetic/immunological response to her clear cell renal carcinoma in the setting of chronic elevated VEGF might have also resulted in the subsequent development of a lymphoid malignant clone.

Conclusion

To the best of our knowledge, this is the first reported case of coexisting NHL, RCC, and VHL disease. The role of a defective pVHL causing increased VEGF expression may provide a potential explanation for this association.

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