Inflammatory Arthritis in a 19-month-old with Von Hippel-Lindau Disease

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ABSTRACT

Von Hippel-Lindau disease (VHL) is a rare autosomal dominant disease characterized by progressive development of cysts and tumors. Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disorder and the most common arthritis in children. Although the mechanism of pathogenesis is not fully understood, JIA is thought to be a polygenic, autoimmune-mediated disease. Inherited or acquired disorders resulting in immune dysregulation can lead to neoplastic and autoimmune disease, but very few cases of patients with VHL and concomitant autoimmune disease are reported in the literature. Herein, we describe, to the best of our knowledge, the first reported case of a child with VHL and inflammatory arthritis, and we discuss three possible pathophysiologic mechanisms that could link VHL and JIA. Understanding the shared pathophysiology and genetics of both diseases may help guide future direction of targeted therapies and lead to improved clinical outcomes.

KEYWORDS: Von Hippel-Lindau disease; inflammatory arthritis; autoimmune disease; immune dysregulation; neoplastic disease; pediatrics

BACKGROUND

Juvenile idiopathic arthritis (JIA) is the most common type of arthritis in children. Oligoarticular JIA is the most prevalent subgroup of JIA,[1] and involves <5 joints.[2] It has an estimated annual incidence of 5-20 cases per 100,000 children.[1,3] The peak age of onset is 1 to 3 years and females are affected twice as frequently as males.[4] Treatment involves intraarticular glucocorticoids, nonsteroidal anti-inflammatory drugs and disease-modifying antirheumatic drugs (e.g., methotrexate).[5–9] Biologic agents (e.g., infliximab) are usually reserved for children with uveitis or extensive joint involvement.[6,10,11]

Von Hippel-Lindau disease (VHL) is a rare autosomal dominant disease characterized by progressive development of cysts and tumors including hemangioblastomas, renal cell carcinoma, pheochromocytoma, pancreatic neuroendocrine tumors, and cysts of the genitourinary tract. It results from a germline pathogenic variant (sequencing change or deletion) in the VHL gene. VHL is a tumor suppressor gene on the short arm of chromosome 3.[12,13] The incidence of VHL is 1 in 36,000 live births with the mean age of symptom onset at 26 years.[14]

There are very few reports of patients with VHL and concomitant autoimmune disease.[15,16] In this report, we present the first reported case of inflammatory arthritis in a 19-month-old female with VHL to highlight possible shared pathophysiologic mechanisms as an exciting area for further study and potential therapeutic development for both diseases.

CASE REPORT

A previously healthy 19-month-old female with no significant past medical history presented to the emergency department for left elbow pain and swelling after falling from a chair. Radiographic imaging showed a non-displaced type 1 supracondylar fracture. After a one-month immobilization period, her course was complicated by an elbow contracture and limited range of motion (ROM) for which she underwent arthrogram and manipulation under anesthesia. The arthrogram revealed no fractures, loose bodies, or elbow instability. Her elbow was immobilized at full extension for one month. Three months later, her ROM decreased again, prompting an MRI that demonstrated a joint effusion with synovial proliferation suggestive of inflammatory arthritis. She was referred to pediatric rheumatology for further evaluation.

Labs were notable for an ANA titer of 1:640 in a homogeneous pattern. C-reactive protein and erythrocyte sediment rate were elevated at 58 mg/L and 35 mm/h respectively. ANA titer 2 was 1:640 in a speckled pattern. Her rheumatoid factor was negative. CBC was unremarkable aside from an elevated platelet count of 475 x10^9/L.

One week after her initial evaluation by pediatric rheumatology, she developed non-traumatic swelling of her right knee and a prominent limp. Radiographic imaging revealed a joint effusion. Joint aspiration showed inflammatory synovial fluid with a white blood cell count of 6,960 cells/uL and no crystals. Lyme serology was negative. She was diagnosed with JIA and started on naproxen and weekly methotrexate (5 mg) with significant improvement in her symptoms. After 20 months of methotrexate treatment, she completed a methotrexate wean due to tolerability issues and stable

disease without active inflammation, synovitis, or uveitis. She did well off methotrexate for 15 months before she presented with active arthritis in her right knee. She had an intraarticular steroid injection in her knee with improvement in her swelling and pain. She restarted methotrexate (7.5 mg weekly) and has not had recurrence of her arthritis.

When she was 4 years old, our patient was referred to genetics for concern of VHL. Her family history was significant as her 30-year-old biological father, paternal grandmother, and 12-year-old paternal half-brother have VHL. No family member with VHL had a known history of inflammatory arthritis or autoimmune soft tissue disease. She completed single site testing for VHL and was found to harbor the pathogenic variant in VHL, c.448_449del (p.Asn150Tyrfs*23), confirming her diagnosis of VHL. There are specific childhood surveillance recommendations for VHL, and these were initiated in our patient. Plasma metanephrine (0.27 nmol/L) and normetanephrine (0.65 nmol/L) levels were within normal limits. She currently has no physical manifestations of VHL and continues to be followed per VHL Alliance Surveillance Guidelines and National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.[17,18]

DISCUSSION

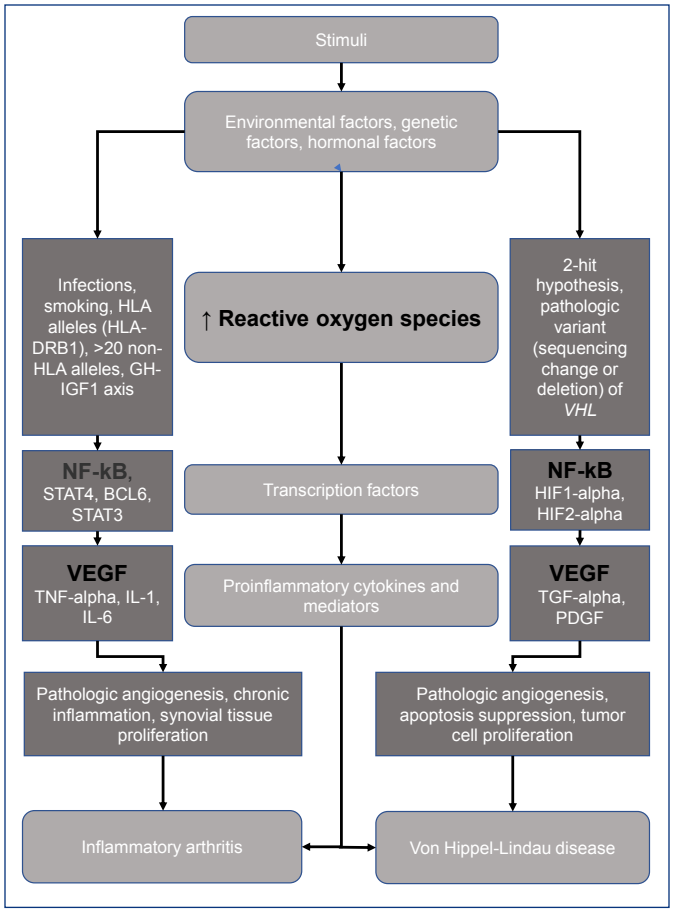
The case presented in this study is the first to show an unusual and previously unreported association between two very different disease processes: inflammatory arthritis and VHL in a young child. Although pure coincidence is possible, it is also possible that a pathologic variant of VHL contributed to the development of inflammatory arthritis in our patient. Based on the incidence of JIA in females under 5 years old (12.2 per 100,000)[3] and the incidence of VHL (1 per 36,000),[14] the likelihood of pure coincidence explaining our patient's co-occurring diseases would be approximately one in 300 million. Thus, the probability of chance alone explaining our patient's presentation is extremely low, but it is not zero.

A review of the literature found several possible pathophysiologic mechanisms including overproduction of reactive oxygen species, dysregulation of the NF-kB signaling pathway, and pathogenic angiogenesis that could link VHL and inflammatory arthritis in children (**Figure 1**). The causal link between VHL and inflammatory arthritis has not been established but may be due to changes in the cytokine milieu with dysfunction of NF-kB, overproduction of reactive oxygen species and pathologic angiogenesis leading to worsening inflammatory arthritis.

Reactive Oxygen Species

Reactive oxygen species (ROS) are oxygen-derived free radicals that are endogenously produced in the mitochondria and play an essential role in oxidative stress. ROS are a natural byproduct of energy metabolism, and their accumulation

Figure 1. Overproduction of reactive oxygen species, dysregulation of the NF-kB signaling pathway, and pathogenic angiogenesis play important roles in the pathophysiology of VHL and inflammatory arthritis. Examples of environmental, genetic, and hormonal factors, transcription factors, proinflammatory cytokines and mediators in both diseases are included.



can lead to cellular damage. They also induce tumorigenic functions such as proliferation and metastasis.[19] ROS play an important role in the pathogenesis of VHL. In cells that lack VHL, hypoxia-inducible transcription factor alpha (HIF1-alpha) is relatively stable irrespective of changes in oxygen, leading to constitutive activation of hypoxia-inducible genes despite normal oxygen levels. This causes ROS accumulation.[20] Additionally, patients with VHL show downregulation of key antioxidant enzymes in charge of ROS homeostasis.[21] The role of ROS in inflammatory arthritis has also been studied with Lipinska et al, showing that the imbalance between the production of ROS and their neutralization leads to oxidative stress. Children with JIA have higher serum concentrations of nitric oxide (NO) end products (a measure of oxidative stress), suggesting that overproduction of NO is involved in the pathogenesis of inflammatory arthritis in children.[22] HIF-alpha is a transcription factor that has been the target of therapies to treat renal cell carcinoma in VHL[23] and many studies show

that HIF-alpha also plays an important role in the pathogenesis of inflammatory arthritis by inducing the production of inflammatory cytokines and autoantibodies.[24,25]

Nuclear Factor Kappa B (NF-kB) Signaling Pathway

NF-kB is a family of transcription factors that play essential roles in apoptosis and inflammation. In normal cells, NF-kB activation is a highly regulated process that controls DNA transcription, cytokine production and cell survival. Disruption of the NF-kB [24,25] absence of functional VHL, expression of NF-kB is enhanced which leads to impaired apoptosis and tumor progression.[26,27] Approximately 70% of patients with VHL develop renal cell carcinoma (RCC) by the age of 60, and the NF-kB signaling pathway has become an exciting target for treatment of RCC in these patients.[28-30] Studies have shown that RCC cells that lack functional VHL have significantly higher expression and activity of NF-kB than RCC cells with functional VHL.[31] NF-kB has also been identified as a pivotal regulator of inflammation in RA.[32] There is increasing evidence that NF-kB activation plays an integral role in the initiation and perpetuation of chronic inflammation in inflammatory arthritis.[33,34] In fact, activated NF-kB has been found in the synovial tissue of patients in early stages of joint inflammation and in those with late-stage disease.[35]

Angiogenesis and Vascular Endothelial Growth Factor

Angiogenesis is the process of new blood vessel development, which is essential for normal physiological functioning as well as pathological processes such as synovial inflammation in inflammatory arthritis and tumor progression in VHL.[36,37] The vascular endothelial growth factor (VEGF) signaling pathway plays pivotal roles in regulating angiogenesis.[36–38] In JIA, there is strong correlation between the expression of VEGF and the inflammatory activity of affected joints.[39] Additionally, increased serum levels of VEGF in children with inflammatory arthritis strongly correlate with disease activity.[40] In VHL, inactivation of the VHL gene leads to pathologic and dysregulated angiogenesis by causing constitutive activation of HIF1-alpha which in turn, upregulates VEGF. VEGF is highly expressed in many of the tumors seen in VHL and targeted therapies with anti-VEGF antibodies (i.e., bevacizumab) are currently in clinical trials. Belzutifan, a HIF2-alpha inhibitor, was recently approved by the FDA for patients with RCC associated with VHL.[41] Belzutifan interrupts pathologic angiogenesis by inhibiting HIF2-alpha and downregulating angiogenesis. Anti-angiogenic therapies are also increasingly recognized as important targets for the treatment of adults and children with inflammatory arthritis, and clinical trials are ongoing.[42]

Overproduction of ROS, impaired NF-kB signaling, and pathogenic angiogenesis play important roles in the pathophysiology of VHL and inflammatory arthritis. Genetic susceptibility may also contribute to the pathogenesis of both diseases. The genetics of VHL is well established; in contrast, JIA is polygenic with multiple HLA alleles and >25 non-HLA susceptibility loci associated with the disease.[43–45] Genome-wide association studies have led to a better understanding of the genomic architecture influencing the risk of JIA and have identified numerous susceptibility loci. Our report highlights three possible associations between the pathogenesis of inflammatory arthritis and VHL. Understanding the shared pathophysiology and genetics of both diseases may help guide future direction of targeted therapies and lead to improved clinical outcomes.

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Disclosures

Funding: No financial support was received for this case report.

Declarations: The present study was exempt from review by the Institutional Review Board of The Warren Alpert Medical School of Brown University and Lifespan Health System.

Consent for publication: Written informed consent was obtained from the patient's parents regarding the publication of this case report.

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