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Case Report Open Access

Prevalence of Hepatocyte Growth Factor and Autoantibodies to α-HGF as a New Etiology for Bilateral Diffuse Uveal Melanocytic Proliferation Masquerading as Neovascular Age-Related Macular Degeneration

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Abstract

Objective: The goal was to test the hypothesis that high serum hepatocyte growth factor (HGF) and retinal autoantibodies against α-HGF contribute to the pathology of bilateral diffuse melanocytic proliferation (BDUMP).

Methods: Case report of an elderly man diagnosed with neovascular age-related macular degeneration (n-AMD) treated with bilateral Bevacizumab injections. Examination included comprehensive ophthalmic examination and images obtained by fundus photography, fundus autofluorescence, fluorescein angiography, spectral-domain optical coherence tomography (OCT), and B-scan ultrasonography. The levels of HGF and circulating HGF receptor (c-MET) were measured in the serum by ELISA and anti-retinal autoantibodies by western blotting.

Results: Patient received Bevacizumab injections for presumed n-AMD and had a history of papillary renal cell carcinoma stage 4 with a tumor containing gene mutation Y1230C in the mesenchymal-epithelial transition factor (MET). Visual acuity was 20/200 OD and CF OS. Multimodal imaging was consistent with BDUMP. Plasma exchange therapy was recommended but could not be started until 10 months later due to deterioration in his medical condition. Pre- and post-plasma exchange sera demonstrated anti-retinal autoantibodies against 69-kDa protein of the same molecular weight as the α-HGF. Serum autoantibodies reacted with purified recombinant α-HGF on the blot.

Conclusions: BDUMP can mimic n-AMD, which can delay treatment. Plasma exchange resulted in resolved inflammation, resolution of exudative detachments and improved vision after cataract surgery. Consideration of the tumor genetics led to the recognition of elevated HGF levels and autoantibodies to α-HGF (anti-69-kDa), which suggested a new pathogenic mechanism of BDUMP. We believe that therapy with tyrosine kinase inhibitors and a checkpoint inhibitor may contribute to the high HGF levels and subsequent immune response.

Keywords: BDUMP; HGF; Autoimmunity; Cancer; Tyrosine kinase inhibitors; HGF receptor (c-MET)

Introduction

BDUMP is a rare paraneoplastic condition [1] with increasing incidence that may masquerade as n-AMD, resulting in delayed diagnosis and treatment. Autoimmune response is highly likely and a serum factor in BDUMP patients has been shown to induce cultured melanocyte elongation and proliferation [2,3]. Multimodal imaging facilitated the diagnosis. In our study, consideration of tumor genetics led us to evaluate serum retinal autoantibodies and levels of HGF and c-MET before and after treatment with plasma exchange.

Report of a Case

A 74-year-old elderly white man complaining of blindness, photophobia and scotomas presented to Retina Associates of Sarasota one month after bevacizumab injection in each eye. Twenty-six months earlier a robotic right partial nephrectomy was performed. Ten months after procedure, CT scanning and biopsy demonstrated Stage 4 papillary renal carcinoma with a MET gene mutation Y1230C. Initially, the patient was treated with tyrosine kinase inhibitors (Pazopanib and later Sorafenib), and then due to side effects, he was switched to an anti-PD-1 antibody check point inhibitor (Nivolumab). Two months later, he was diagnosed with n-AMD and given a Bevacizumab injection in each eye. Nivolumab was discontinued after four months due to side effects and Axitinib (a tyrosine kinase inhibitor) was initiated, and the patient has continued on this medication.

At presentation, vision was 20/200 OD and CF OS. Intraocular pressure was low (8 mmHg OD and 6 mmHg OS). The anterior segment had dilated episcleral vessels but no abnormal pigmentation in either eye. The corneas were clear and the anterior chambers were deep and quiet. The irides were normal and there were no nevi or masses. The lenses had moderate nuclear sclerosis. Both eyes had a posterior vitreous detachment but no vitreous cells. The fundus examination in each eye demonstrated multiple nevi and many round reddish patches with sub-retinal fluid in the macula and shifting exudative retinal detachments in the inferior periphery OU. Color

fundus photography revealed multiple pigmented nevi OU and round reddish islands of retinal pigment epithelium (RPE) separated by a pattern of polygonal orange pigmentation (Figures 1A and 1B). Fundus autofluorescence (30° Heidelberg Retinal Angiograph; Heidelberg Engineering) demonstrated increased levels of autofluorescence corresponding to the orange polygonal lesions and decreased levels of expected RPE autofluorescence, corresponding to the round areas of presumed RPE atrophy (Figures 1C and 1D). These round lesions appeared dark on the near infrared images (Figures 1E-F left). Spectral domain optical coherence tomography (OCT) demonstrated macular neurosensory detachment with focal areas of RPE atrophy and hypertrophy OU (Figures 1E-F right). In addition to the highly reflective choroidal nevi, thickened choroid OU was noted on the enhanced depth imaging OCT (EDI-OCT) (Figures 1E-F right). Fluorescein angiography demonstrated transmission defects corresponding to areas of RPE atrophy, blocking corresponding to orange polygonal areas and nevi, and scattered speckled and peripapillary punctate areas of hyperfluorescence. B-scan ultrasonography confirmed the presence of thickened choroid and exudative retinal detachments OU.

BDUMP was diagnosed based on the history, ophthalmic examination and multimodal imaging. Plasma exchange was recommended but could not be started until ten months later due to deterioration in his medical condition. The highest HGF levels were present in pre-plasma exchange at 1990 pg/ml and then lowered after plasma exchange (681 pg/ml), and in final post-plasma exchange dropped to 452 pg/ml. No circulating HGF receptor (c-MET) was detected. Pre- and post-plasma exchange fluid demonstrated anti-retinal autoantibodies against 69-kDa protein of the same molecular weight as α-HGF. Serum autoantibodies were found to react with a purified recombinant α-HGF on the blot. Plasma exchange resulted in reduced inflammation, resolution of exudative detachments and improvement in vision after cataract surgery. Multimodal imaging demonstrated the progression of RPE atrophy (Figures 2A and 2B), nevi growth (Figures 2C and 2D), resolution of neurosensory detachments (Figures 2E-F left) and stable choroidal thickening on EDI-OCT (Figures 2E-F right). Nineteen months after presentation (5 months after finishing plasma exchange), visual acuity was 20/40+2 OD and 20/50+2 OS.

Discussion

BDUMP is a rare ocular paraneoplastic syndrome that may masquerade as n-AMD, resulting in delayed diagnosis and treatment [4]. The observation that approximately 40% of BDUMP cases occur prior to the diagnosis of the primary cancer and that BDUMP patients often present with advanced cancer suggests the potential for autoimmunity to contribute both to the survival and to the paraneoplastic process [4]. The etiology of the syndrome is not understood. Plasma exchange improves the signs and symptoms of BDUMP [5]. Recent studies showed that the plasma IgG fraction caused melanocyte elongation and migration [2]. However, a specific factor that could contribute to pathology of the syndrome has not been identified [3]. We believe that our study further elucidates a possible mechanism of BDUMP, by showing high levels of α-HGF combined with likely autoantibody response to the α-HGF (69-kDa).

An array of seemingly unrelated tumors can rarely be associated with BDMUP, including ovarian, lung, gallbladder, cervical, uterine, kidney, pancreatic, breast, esophageal/gastric and colorectal cancer [6]. All of these tumors have been found to have concomitant elevation of serum HGF in some patients and HGF can be delivered from remote tissues through the circulation [7]. Excepting pancreatic, these cancers have been known to rarely have MET gene mutations. Although pancreatic cancer remains the exception, MET gene dysregulation and elevated HGF levels have been found to lead to poor prognosis in pancreatic cancer [8]. Non-small cell lung cancer has been known to have the Y1230C mutation at a very low frequency (mutant allele frequency=0.3%).

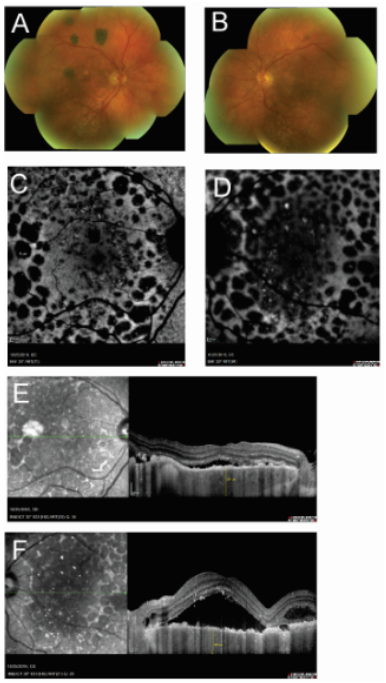

Figure 1: Multimodal Imaging of the Retina Prior to Plasma Exchange A and B, Color fundus montage of the right (A) and left (B) eye showing showing multiple nevi, orange polygonal pigment and round reddish lesions. C and D: fundus autofluorescence (30° Heidelberg Retinal Angiograph; Heidelberg Engineering) demonstrating increased autofluorescence corresponding to the polygonal pigment and absence of autofluorescence corresponding to the round areas of presumed RPE atrophy. E-F left: near infrared images showing the dark round lesions corresponding to presumed RPE atrophy and a bright lesion in the right eye corresponding to a choroidal nevus. E-F right: spectral domain (OCT) demonstrated macular neurosensory detachment with focal areas of RPE atrophy and hypertrophy, and a highly reflective choroidal nevus in the right eye; enhanced depth imaging optical coherence tomography (EDI-OCT) demonstrated thickened choroid in both eyes.

Consideration of our patient's papillary renal-cell carcinoma tumor activating missense mutation (Y1230C) in the tyrosine kinase domain of the MET gene [9] led to the hypothesis that BDUMP is caused by retinal autoantibodies to α-HGF. The MET gene encodes the receptor for HGF (c-MET). HGF is made of a 69-kDa α-chain and a 34-kDa β-chain. Previous 2 reports of circulating anti-retinal autoantibodies in BDUMP patients were positive for recoverin (23-kDa) and a 70-kDa protein thought to be Heat Shock Protein (HSP70) in one case, and 33-kDa and 34-kDa in the second case [5,10]. We found elevated level of α-HGF in our patient and identified α-HGF as the retinal protein

reacting with the anti-69-kDa retinal autoantibodies present in the serum.

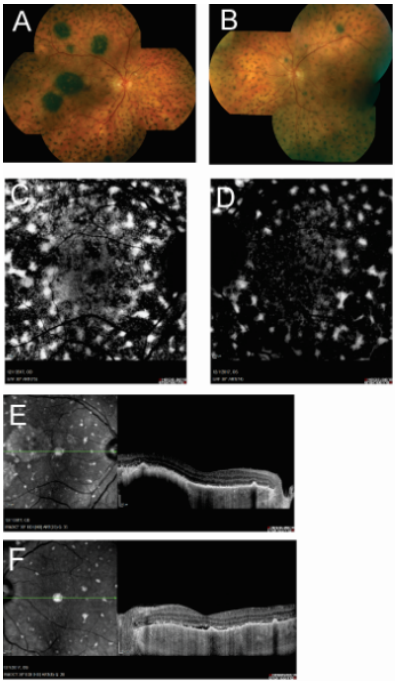

Figure 2: Multimodal imaging of the retina after plasma exchange A and B, Color fundus of the right (A) and left (B) eye showing showing enlarged multiple nevi, contracted orange polygonal pigment and increased pigment clumping. C and D: fundus autofluorescence (30° Heidelberg Retinal Angiograph; Heidelberg Engineering) demonstrating increased autofluorescence corresponding to the polygonal pigment and increased absence of autofluorescence corresponding to presumed RPE atrophy. E-F left: near infrared images showing loss of the dark round lesions and enlarged bright lesion in the right eye corresponding to a choroidal nevus. E-F right: spectral domain (OCT) demonstrated resolved macular neurosensory detachment with focal areas of RPE atrophy and hypertrophy, and an enlarged choroidal nevus in the right eye; enhanced depth imaging optical coherence tomography (EDI-OCT) demonstrated stable thickened choroid in both eyes.

It is possible that chronic high levels of HGF in combination with retinal autoantibodies may drive the choroidal nevi growth and RPE damage seen in BDUMP. In donor eyes, the RPE layer is the most positive site for c-MET (HGF receptor) expression [11] HGF stimulation of melanocytes up-regulates c-MET expression [12], promotes melanocyte proliferation and motility [13], stimulates RPE proliferation and migration during wound healing [14] and, in proliferative vitreoretinopathy models, induces RPE separation and dedifferentiation [15]. High serum levels of HGF have been associated with metastasis and reduced survival in cancer patients [8].

The reason for the doubling in incidence of BDUMP over the past decade is unclear. In addition to increased awareness, an improved identification with multimodal imaging, longer patient survival, and new therapies may contribute to increase incidence. Tyrosine kinase inhibitors can increase HGF levels [16]. Checkpoint inhibitors, such as Nivolumab, have been associated with ocular immune dysfunction manifesting as Vogt-Koyanagi-Harada-like choroidal thickening, choroidal effusions and keratitis [17-19]. In conclusion, our study shows for the first time that BDUMP was associated with high levels of HGF as well as anti-retinal autoantibodies against α-HGF (69-kDa). Therapy with a tyrosine kinase inhibitor (Pazopanib, Sorafenib, Axitinib) and a checkpoint inhibitor (Nivolumab) may contribute to the high HGF levels and the immune response. These results suggest a new etiology related to high levels of HGF combined with an autoimmune response to the α-HGF (69-kDa) in the pathogenesis of BDUMP.

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Conflicts of Interest

The authors have no financial or conflicts of interest to disclose.

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