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Retinopathy in a Patient with Influenza-Associated Pancytopenia

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Introduction

Retinal abnormalities have been widely recognized as potential signs of hematologic disturbances, particularly in anemic and thrombocytopenic patients. Retinopathy in such cases is generally asymptomatic and characterized by retinal hemorrhage, cotton-wool spots attributed to retinal hypoxia, retinal edema, and hard exudates often from resolved edema.[1] Anemia has been reported to cause retinopathy in nearly a third of patients, particularly those who have coexisting thrombocytopenia.[2] Pancytopenia, low levels of all three hematologic cell lines, is an uncommon consequence of systemic infection, and influenza-associated pancytopenia has rarely been characterized in the literature. Limited reports have described pancytopenia due to hemophagocytic syndrome secondary to influenza in pediatric patients with underlying acute leukemia,[3] while another case presented a patient with pancytopenia after streptococcal pneumonia superinfection.[4] Resolution of retinopathy associated with hematologic disturbances is closely tied to successful treatment of underlying abnormalities. Herein, we present a unique case of influenza-associated pancytopenia causing prolonged retinopathy that fully resolved despite in the presence of untreated pancytopenia.

Case Report

A 14-year-old female with history of asthma presented to the emergency department after an episode of diffuse leg weakness and near syncope. The patient reported one week of fatigue with intermittent shortness of breath which did not resolve with nebulizer treatments. She denied other symptoms including fever, congestion, cough, and sore throat but endorsed that she was on day two of an unusually heavy menstrual period.

On admission, the patient was found to be profoundly pancytopenic (white blood cells [WBC] 2.2 [5.5-15.5 $x10^9$/L], absolute neutrophil count [ANC] 300 [2500-6000 cells/mcL], platelets 9 [150-450 $x10^9$/L], red blood cells [RBC] 1.77 [4.10-5.40 $x10^{12}$/L], and hemoglobin [Hb] 3.0 [11.0-14.5 g/dl] with mixed areas of acellularity on bone marrow biopsy. She was transfused with two units packed RBC and one unit of platelets and received oseltamivir phosphate (Tamiflu, Genentech, San Francisco) for influenza and intravenous aminocaproic acid for heavy menstrual bleeding. Shortly after admission, she noted decreased visual acuity in both eyes. Presenting visual acuity was 20/200 in the right eye and 20/60 in the left eye. Intraocular pressures, pupillary exam, extraocular motility, and confrontation visual fields were normal. Ophthalmic exam revealed diffuse intraretinal hemorrhages in both eyes with Roth spots scattered in the midperipheral and peripheral retina, likely secondary

to anemic retinopathy. Initial imaging showed some hemorrhage surrounding the optic disc, as well as intraretinal hemorrhage along the retinal vasculature and within the temporal vascular arcades (Figures 1A-B, Figures 2A-B).

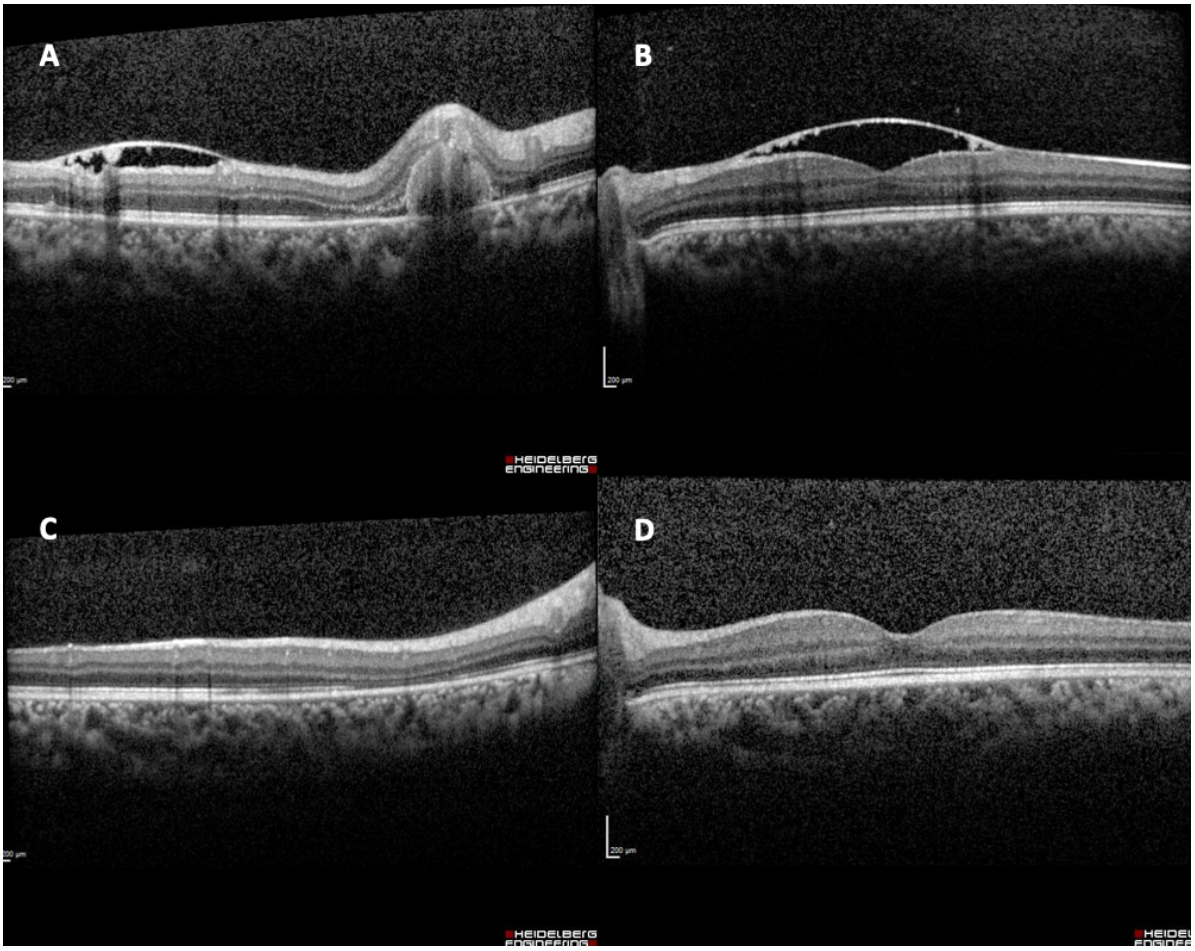

Figure 1. Optical coherence tomography of right eye (A) and left eye (B) at presentation showing subhyaloid hemorrhage in both eyes and an area of subretinal hemorrhage in the right eye. Optical coherence tomography of right eye (C) and left eye (D) showing complete resolution seven months later.

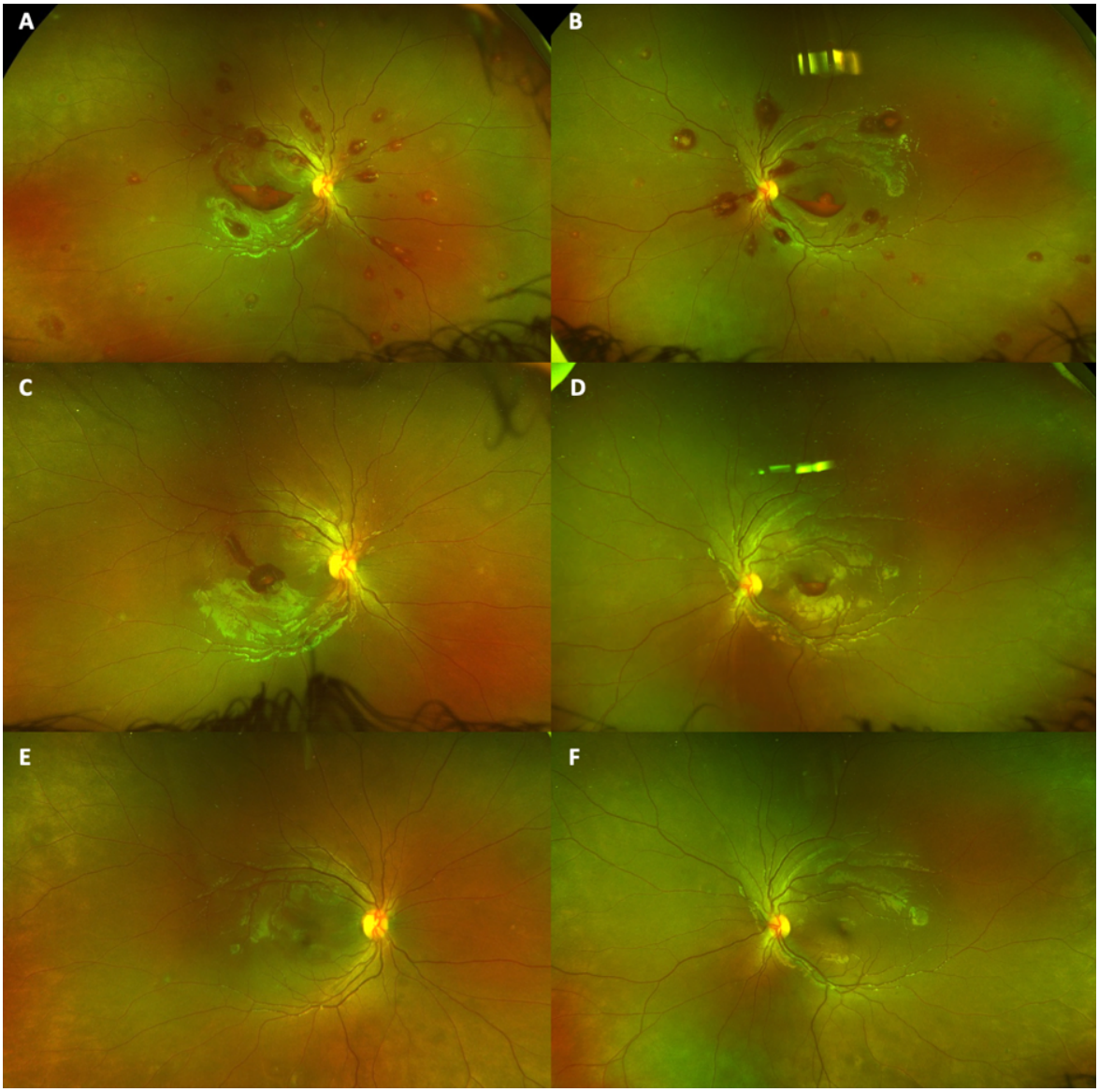

Figure 2. Color fundus photos of right eye (A) and left eye (B) at presentation showing intraretinal hemorrhage overlying the macula and Roth spots in the midperipheral and peripheral retina. Photos of right eye (C) and left eye (D) two months later showed significant improvement but with persistent hemorrhage overlying the macula that limited visual acuity. Fundus photos seven months later of right eye (E) and left eye (F) showed complete resolution of the hemorrhage.

Over seven months, the patient remained pancytopenic and received several transfusions as an outpatient. Although lab values improved slightly, they never returned to normal. Hematologic workup revealed normal cytogenetics, no paroxysmal nocturnal hemoglobinuria, negative Fanconi anemia testing, normal telomere length, negative anti-nuclear antibody, and negative CD34 staining. She tested negative for hepatitis A, hepatitis B, human immunodeficiency virus (HIV), parvovirus B19, and cytomegalovirus. The patient's hemoglobin profile was normal with slightly elevated fetal hemoglobin, likely reflecting stress hematopoiesis from pancytopenia. Peripheral blood smear showed no schistocytes, sickle cells, blasts, or abnormal WBC. Coagulation studies uncovered slightly low activated partial thromboplastin time of 21.8 [25.1-36.5 seconds], elevated prothrombin time of 13.1 [9.8-12.8 seconds], and international normalized ratio of 1.15 with normal fibrinogen levels, making disseminated intravascular coagulation unlikely. She denied recent medication use,

toxic exposure, or radiochemotherapy. She was ultimately diagnosed with severe aplastic anemia associated with influenza A and immunosuppressive therapy was recommended, which her mother declined due to concern about possible side effects. Despite remaining pancytopenia, with WBC 2.2 $x10^9$/L, ANC 200 cells/mcL, platelets 11 $x10^9$/L, RBC 2.09 $x10^{12}$/L, and hemoglobin 7.2 g/dL, the hemorrhage completely resolved without recurrence in both eyes and visual acuity stabilized at 20/25 in both eyes seven months later (Figures 1C-D, Figures 2C-F).

Discussion

Influenza-associated pancytopenia is rare, with few cases documented in the literature. Of previously reported cases, three patients with influenza-associated pancytopenia had an underlying acute leukemia which further predisposed them to systemic hematologic abnormalities, while another involved a patient with a comorbid bacterial superinfection.[3,4] Though aplastic anemia has been linked to systemic infection with viruses such as hepatitis, Epstein-Barr, cytomegalovirus, HIV, and parvovirus B19, influenza is not strongly associated with hematologic disturbances in previously healthy individuals.[5] This case highlights the possibility that even young, healthy patients without predisposing immunocompromising conditions may develop persistent severe aplastic anemia and associated ophthalmic sequelae.

While retinopathies associated with pancytopenia and other hematologic abnormalities have been well-documented in the literature, previous reports have emphasized that resolution of retinopathy occurs with successful treatment of underlying cytopenias.[6-8] This case reported herein was complicated by the family's decision to decline the recommended immunosuppressive therapy for severe aplastic anemia. Despite remaining pancytopenic for over seven months, the retinal hemorrhage completely resolved and visual acuity improved in both eyes. This suggests that the interplay between pancytopenia and retinopathy may invite further investigation.

The risk of retinopathy in anemic patients rises as the severity of anemia grows, with a worse prognosis when hemoglobin is below 6 g/dL at presentation, as in this patient.[2] Anemia contributes to retinal hypoxia, leading to two downstream effects: vascular dilation causing retinal edema and hemorrhage, and nerve fiber layer infarction manifesting as cotton-wool spots.[9] Thrombocytopenia exacerbates these issues via abnormal coagulation. White-centered Roth spots may develop due to the presence of inflammatory infiltrates or focal areas of ischemia.[9] Resolution of this type of retinopathy is multifactorial and varies from patient to patient. Previous studies have suggested that retinal damage may depend on hemorrhage size and ability to clear the blood.[10] The mechanism of retinal hemorrhage reabsorption is unclear, with little exploration of proposed pathophysiology in the literature, but typically tracks with hematologic treatment. Platelets release trophogens and growth factors that maintain the structural integrity of the vascular endothelium during normal remodeling.[11] In clinically significant thrombocytopenia, low levels of platelets lead to a reduction of these factors, causing disassembly of the complexes maintaining the vascular endothelium intercellular barrier and, subsequently, hemorrhage.[11] One hypothesis for why this patient's hemorrhage resolved without systemic immunosuppresion is that her platelet count rose enough to produce a sufficient level of trophogens to begin to stabilize the endothelium again, allowing macrophages to clear existing hemorrhage. There is no known minimum platelet value to regain this function.

Upon resolution of retinopathy, the patient remained severely anemic with hemoglobin below 8 g/dL and platelet count under 150 x 10^9/L, which have both been identified as predictors of retinopathy.[2,12] While cell counts remained low over her clinical course, the parameters have remained stable despite consistent

transfusions which may have allowed natural adaptive mechanisms to reabsorb the hemorrhage. A thorough literature review finds that there is no hemoglobin or platelet value reported at which hemorrhage resolves.

Conclusion

This case offers a perspective on the relationship between influenza and pancytopenia and discussed the standard management of retinopathy due to hematologic disorders. The patient fully recovered vision despite prolonged retinopathy with ongoing pancytopenia, and this emphasizes the need for further investigation into the relationship between viral infection, systemic hematologic effect, and retinal involvement. The current standard practice for patients with retinopathy due to underlying anemia is to observe, as resolution has traditionally aligned with a return to normal hematologic value, and often improvements on fundus exam imply improvement in the underlying condition.[10] This case, however, demonstrates that even when there is only partial improvement in severe pancytopenia, retinal hemorrhage may still reabsorb.

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Statement of Ethics

This case report was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient health information was performed in a Health Insurance Portability and Accountability Act (HIPAA) – compliant manner. Informed consent was obtained prior to performing the procedure, including permission for publication of all photographs and images included herein.

Conflict of Interest Statement

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