Multiple autoimmune syndrome complicating the management of diabetic retinopathy

Anmar Abdul-Rahman, FRANZCO, MOphth, Consultant Ophthalmologist*

Department of Ophthalmology, Counties Manukau DHB, Auckland, New Zealand

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ABSTRACT

Purpose: To describe a case of multiple autoimmune syndrome presenting with type I diabetes, choroidal vitiligo, coeliac disease, pseudohypoparathyroidism, and immune thrombocytopenia purpura (ITP), the latter diagnosed seven years after the initial presentation.

Observations: A 26-year-old female presented with bilateral severe diabetic retinopathy. Panretinal photocoagulation (PRP) was initially declined due to poor adherence to treatment. Thirty-three months after the initial presentation, a progression of the retinal disease to bilateral proliferative retinopathy, macular edema, and epiretinal membranes was noted. Additionally, an ischemic branch retinal vein occlusion was diagnosed in the inferior nasal quadrant of the left eye. Over this period visual acuity declined from 6/9 bilaterally to 6/24 and 6/30 in the right and left eyes, respectively. PRP was then performed under subtenons anesthesia. Excessive hemorrhage was noted from the site of the conjunctival wound, and Tranexamic acid was prescribed post-operatively. Investigations did not reveal a primary coagulopathy. Seven years after the initial presentation, the patient was admitted to hospital with a spontaneous right frontal lobe intracerebral hemorrhage, from which a recovery occurred without neurologic deficit. Hematological parameters remained normal for this admission and the cause of the spontaneous hemorrhage remained undiagnosed. Seven months after this episode, the patient was admitted to the Hematology ward after a five-week history of gingival hemorrhage subsequent to a dental procedure. As the platelet count was $16 \times 10^9/L$, a diagnosis of ITP was confirmed. However, the platelet count failed to respond to treatment with Prednisone, intravenous Immunoglobulin, Tranexamic acid, Eltrombopag, and Rituximab. A second fatal intracranial hemorrhage occurred two months later.

Conclusion and Importance: Multiple autoimmune syndrome may complicate the presentation and management of diabetic retinopathy. In some cases, the manifestations of systemic autoimmune disease may dominate the clinical picture. Management of the more complex disease burden, in this case, became an increasingly perplexing multidisciplinary predicament with each additional autoimmune disorder diagnosed over the treatment course.

1. Introduction

Overlap of the pathophysiological mechanisms of autoimmune diseases can result in the co-existence of several disease subtypes in the same patient. Rojas et al. reported polyautoimmunity in more than one-third of patients already diagnosed with one autoimmune disorder.1 There is a growing body of evidence of an increased incidence of polyautoimmunity that has been expanding to include endocrine, rheumatologic, gastrointestinal, and neurological disorders.2–7 Autoimmune thyroid disease and Sjögren’s syndrome are among the most frequently encountered co-associated diseases and patients with these disorders both commonly present with ophthalmic manifestations.8

First described by Pirofsky and Vaughn in 1968, the co-existence of three or more autoimmune diseases is known as multiple autoimmune syndrome (MAS).9,10 There is limited information in the ophthalmic literature on the prevalence of MAS in patients with an autoimmune disease with primary ophthalmic manifestations. In the largest study to date of a cohort of 3209 patients with Graves’ disease (984 with Graves’ ophthalmopathy) 16.7% of patients had another associated non-thyroid autoimmune disease, and MAS was reported in 1.5% of patients with this disorder. The occurrence of MAS was significantly higher (p-value = 0.02) among patients with Graves’ ophthalmopathy (18.9%) than...
with those without eye disease (15.6%). Several investigators have reported co-existing autoimmune disorders associated with myasthenia gravis (MG) and of these, autoimmune thyroid disease was the most frequent, occurring in 10% of MG patients. Other common autoimmune associations with MG are systemic lupus erythematosus (1–8%) and rheumatoid arthritis (4%).

Carvalho et al. and Volkman et al. reported an association between adult-onset neumyelitis optica and both Sjogren’s and Nephrotic syndrome, respectively.

Described is a case of MAS with type I diabetes (T1D), choroidal vitiligo, coeliac disease, and immune thrombocytopenia purpura (ITP). The latter was diagnosed after seven years of clinical suspicion of an underlying coagulopathy, which ultimately resulted in a fatal intracranial hemorrhage three months after the diagnosis was established.

I.1. Case report

A 26-year-old female with a background of T1D, which was diagnosed at the age of 12 years, was referred to the Ophthalmology Department for the management of diabetic retinopathy. Choroidal vitiligo was noted on previous retinal photographs (Fig. 1). Past medical history included coeliac disease, pseudohypoparathyroidism, primary hypertension, epilepsy, menorrhagia, frequent ecchymosis with minimal trauma, and excessive bleeding from minor surgical and dental procedures. The patient’s father was investigated for rectal bleeding and died of an undiagnosed coagulopathy. A Hematologist assessed the patient two years prior, however, the suspicion remained low of a hemorrhagic diathesis due to a normal coagulopathy screen. Additionally, a posterior basal ganglia infarct and generalized cerebral atrophy were reported on a magnetic resonance imaging study at this consultation. Hemoglobin A1C was 67 mmol/mol, renal function test, lipid profile and tests during this interval, potential complications were discussed, treatment recommendations were re-enforced and a multidisciplinary team including Psychiatric, Endocrine, and Neurology services was engaged in the patient’s care.

Eventually the patient agreed to undergo bilateral PRP. A PASCAL 532nm Argon slit-lamp pattern laser (TOPCON Medical Systems, Inc., Oakland, NJ, USA) was used to apply 2300–2400 laser spots per eye divided into two sessions. Laser spot settings were 200 μm for 20 ms duration. Laser spot power ranged between 300 and 400 mW. Both a Volk Trans-equator and a Superquad 160 contact fundus lens (Volk, Ohio, USA) were used to visualize the retinal mid and far periphery, respectively. Treatment was performed under subtenons anesthesia. Protracted conjunctival hemorrhage was noted from the site of the conjunctival incision during the procedure in both sessions together with a history of persistent bleeding with surgical procedures, therefore Tranexamic acid 500mg BD for five days was prescribed post-laser and the patient was re-referred to the Hematology Department for suspicion of an underlying coagulopathy. In a virtual consultation, a Hematologist reported a normal platelet count and reaction time, factor VIII, XIII, IX, XI assay, activated partial thromboplastin time, prothrombin time, and fibrinogen levels, Von Willebrand factor antigen, ristocetin cofactor activity, and collagen binding assay were normal. A recommendation was made to cease the use of tranexamic acid due to the lack of investigative evidence of a primary bleeding disorder.

Three years later the patient was admitted to the Emergency Department with a spontaneous right frontal lobe intracerebral hemorrhage. The lesion measured 2 × 3 × 2 cm on CT scan associated with surrounding edema and mass effect in the anterior cranial fossa (Fig. 4-A). Complete blood count, coagulation screen, and platelet function screen were normal and an MRI of the brain failed to reveal a structural intracranial lesion. Therefore an underlying diagnosis for the cause of the hemorrhage was not established. Recovery from this event occurred without residual neurological deficits.

Further vision loss to 6/30 OS was noted in the first follow-up with the Ophthalmology Clinic in three years. This was secondary to an extension of the vitreous hemorrhage, although vitrectomy was recommended, the question of the coagulopathy remained an obstacle for immediate surgical intervention and the procedure was planned after a further medical review. Two months later the patient was admitted to the Hematology ward with protracted bleeding of the gums five weeks after a dental procedure and a drop in the platelet count to 16 × 10^9/L.
Fig. 2. Sequential color fundus images and macular OCT over the course of 33 months from presentation
A) At presentation: Bilateral severe diabetic retinopathy. The left macula showed evidence of an early epiretinal membrane and cystic change at the foveola.
B) At six months: regression of the hemorrhagic change and development of bilateral epiretinal membranes. OCT of the left macula showing macular distortion.
C) At 33 months: Bilateral proliferative retinopathy and macular edema. A fibrovascular complex is visible on the inferior temporal arcade in the right eye. OCT showing bilateral epiretinal membrane with cystoid edema in the temporal macula of the right eye, serous retinal detachment and hard exudate in the temporal macula of the left eye.
was reported. A diagnosis of immune thrombocytopenia purpura (ITP) was then made. Subsequent treatment with Prednisone, intravenous Immunoglobulin, Tranexamic acid, Eltrombopag, and Rituximab failed to stabilize a declining platelet count. Three months later the patient was transferred to the Emergency Department once again after being found unconscious at home. The platelet count had decreased to 1 × 10^3/L. CT scan of the head showed a left frontal lobe intracerebral hematoma measuring approximately 7.8 × 7.1 × 5.1 cm and extending in the left temporal lobe, with surrounding mass effect. There was a midline shift to the right of 2.2 cm, and early hydrocephalus. Blood was also present in the lateral ventricles, subarachnoid space, and extra-axially. Vitreous hemorrhage was noted in the left eye (Fig. 4-B). The patient was admitted to the intensive care unit and intubated, however, the hemorrhage was deemed inoperable and the event was fatal.

2. Discussion

Described is a case of MAS with diabetic retinopathy being the primary ophthalmic presentation. Throughout the natural history of the disease, the clinical course was dominated by progressive ischemic retinopathy and disordered coagulation, the latter dominating the later stages of the clinical course in the form of recurrent intracranial hemorrhage.

T1D is recognized as a common autoimmune disorder. Patients with T1D exhibit an increased risk of other autoimmune disorders such as autoimmune thyroid disease, Addison’s disease, autoimmune gastritis, coeliac disease, and vitiligo. The association of T1D with ITP as a manifestation of the polyautoimmune disease spectrum is less well recognized. In the largest study to date, Kamioka et al. investigated the frequency of latent and overt polyautoimmunity in 47 children and adolescents with ITP of greater than six months duration. The frequency of latent polyautoimmunity was 36.2%, and, of overt polyautoimmunity was 4.3%. They concluded that children and adolescents with ITP present a high frequency of latent and overt polyautoimmunity and are positive for many autoantibodies other than ANA. Only one patient in this group had T1D as part of the polyautoimmunity spectrum. Rashid et al. described ITP in a case of diabetic nephropathy, which only manifested after renal transplantation. Tshcdin et al. reported two patients with T1D associated with ITP, neither of these two cases presented with ophthalmic manifestations. Kwon et al. reported a case of severe non-proliferative diabetic retinopathy and ITP-associated retinopathy, which ultimately resulted in a poor visual prognosis. There is currently no definitive laboratory test for ITP and it is considered a diagnosis of exclusion. The outcome and prognosis are variable due to a variation in the severity of bleeding at any given platelet count as well as the response to various treatments, complicating the management of this disorder. The aggressive clinical course in the described case may be due to diabetes-related impairment of the coagulation pathways. Dysregulation of the coagulation pathways is known to occur in both type I and type II diabetes, although conventionally, impaired signaling pathways, through multiple mechanisms, lead to an increased tendency to activate and aggregate platelets in response to a given stimulus (platelet hyperreactivity). Also disturbance of other hemorheological parameters in diabetes including hematocrit, plasma proteins, erythrocyte aggregation, and deformability, have been shown to increase both plasma and whole blood viscosity. These factors may have played a role in the pathogenesis of the BRVO observed in the left eye at 33 months follow up. Hemorheologic abnormalities play a controversial role in the pathogenesis of BRVO erythrocyte volume, level of fibrinogen, and hematocrit appear to be important in the pathogenesis. The dual vascular pathology of BRVO and proliferative retinopathy in the left eye indicated a more critical circulatory compromise compared to the right eye and consequently a worse long term prognosis in the left eye.

Structural and functional disturbance of the retinal microcirculation with progressive ischemia include thickened retinal vascular basement membranes, platelet aggregation, leukocyte activation/adherence. These factors may be responsible for the “transitional interval” imaged at six months follow up, which demonstrated regression of the retinal hemorrhage and exudative changes before progression to clinical proliferative retinopathy.

The main limitations in the description of this case are the lack of a diagnosis of the coagulopathy, which manifested in the earlier stages of the disease. This may have represented an unrecognized entity, secondary to autoimmune and/or diabetes-related dysregulation of the platelet-mediated mechanisms in thrombosis. Additionally, fluorescein angiography would have been a useful diagnostic tool in elaborating on the clinical findings. The multifactorial nature of the pathogenesis in addition to the reluctance of the patient to engage with medical personnel added significant complexity to an already perplexing and challenging case.

3. Conclusions

Multiple autoimmune syndrome may complicate the presentation and management of diabetic retinopathy. In some cases, the manifestations of systemic autoimmune disease may dominate the clinical picture. Management of the more complex disease burden, in this case, became an increasingly perplexing multidisciplinary predicament with each additional autoimmune disorder diagnosed over the treatment course.
Fig. 4. Axial brain CT scans showing the two episodes of intracranial hemorrhage A) A right frontal lobe hematoma with surrounding intracerebral edema. B) Massive intracranial hemorrhage involving mainly the left frontal lobe with surrounding intracerebral edema and midline shift. Vitreous hemorrhage was noted in the left eye on both occasions.

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The author attests to satisfying the ICMJE criteria for authorship.

Patient consent
Patient consent could not be obtained. All identifiable patient information has been removed.

Declaration of competing interest
None.

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