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LETTER TO THE EDITOR

Retinal Vasculitis Revealing Immunoglobulin G Subclass Deficiency

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ABSTRACT

Immunoglobulin G (IgG) subclass deficiency is a rare primary immunodeficiency syndrome characterized by recurrent infections and autoimmune disorders. However, there have been no reports of ocular involvement, either inflammatory or infectious, in association with IgG subclass deficiency. The authors report the first case of retinal vasculitis that led to the diagnosis of IgG subclass deficiency, in a patient with a history of inflammatory bowel disease and recurrent infections of previously unknown origin.

KEYWORDS: IgG subclass deficiency, Primary immunodeficiency, Retinal vasculitis

The deficiency in immunoglobulin G (IgG) subclasses is a primary immunodeficiency syndrome, characterized by very low levels of one or more IgG subclasses in the blood. Children and young adults are more commonly affected, with no gender predilection.[1,2] The most common clinical features are recurrent ear and upper respiratory infections, and autoimmune disorders.[1–3] To the best of our knowledge, to date, autoimmune ocular involvement has not been described in association with IgG subclass deficiency. We report the first case of retinal vasculitis revealing IgG subclass deficiency.

OBSERVATION

A 33-year-old woman was referred to our department for blurred vision in the left eye for 15 days. The best-corrected visual acuity was 20/20 OD and 20/25 OS. The slit-lamp examination of the left eye showed the presence of grade 1 anterior chamber inflammation. There were no keratic precipitates or posterior synechia. Fundus examination revealed mild hyalitis associated with cotton-like nodes around vasculitis. These findings were confirmed by fluorescein retinal angiography (Figure 1). The right eye was normal, as was the intraocular pressure in both eyes.

The patient had a more than 10-year history of multiple and apparently idiopathic disorders, including recurrent otitis media, repeated events of herpes zoster on the chest, persistent asthenia, and Raynaud syndrome. There were also recurrent episodes of diarrhea and bowel inflammation, which were believed to be due to an atypical form of Crohn disease.

Clinical examination revealed moderately increased lymph nodes, but no fever or any ongoing cutaneo-mucous, articular, or cardiopulmonary disorder. Blood pressure was 120/70 mmHg. Magnetic resonance imagings of cerebral and optic nerves (MRI) were normal. A colonoscopy was performed. Multiple biopsies revealed no evidence of Whipple disease, Crohn disease, or tuberculosis, and PCR for Whipple disease was also negative on peripheral blood. Moreover, the patient had been treated unsuccessfully with 5-ASA (5-aminosalicylic acid).

An anterior chamber tap was performed and was negative for toxoplasmosis, herpes simplex virus-1 (HSV-1), HSV-2, varicella-zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) infections. Blood serological results were also negative for HIV, HBV, HCV, CMV, Lyme disease, scratch cat disease, syphilis, and brucellosis. Complete blood count was normal, with no biological sign of an ongoing inflammatory syndrome. Angiotensin-converting enzyme and calcium blood

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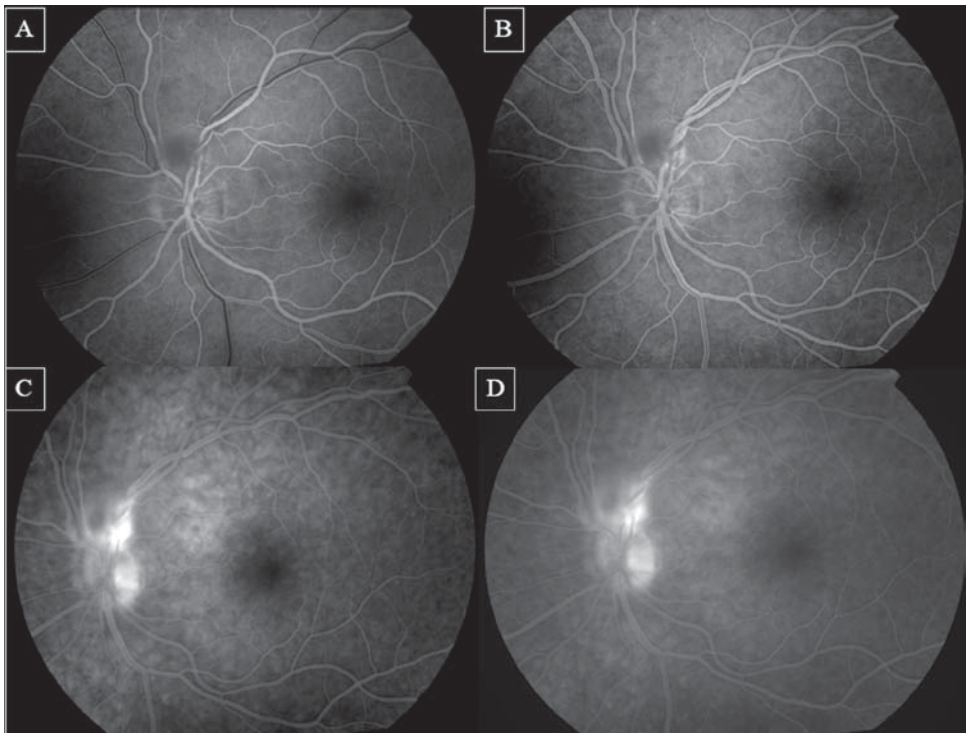

FIGURE 1 Initial fluorescein angiography of left eye. Early fluorescein angiogram shows a supero-papillar area of mask effect. Later phase shows staining of proximal arterio-venous vessels.

level were normal, and autoimmune evaluation, including anti-nuclear antibodies, anti-DNA antibodies, rheumatoid factor, anti-cyclic citrullinated peptide antibodies (anti-CCP), anti-extractable calf thymus antibodies (anti-ECT), and anti-neutrophil cytoplasmic antibodies (ANCA), was also negative. The tuberculin skin test was normal (4 mm). In contrast, plasma protein electrophoresis showed a moderate decrease in gamma-globulins, and measurement of IgG subclasses revealed very low levels of IgG1, IgG2, and IgG3, while levels of IgM and IgA were normal.

The patient was given oral steroids (prednisolone 1 mg/kg/day for 2 months, then slowly tapered over 3 months) to reduce inflammation. After the onset of corticotherapy, consecutive follow-up examinations showed an improvement in visual acuity to 20/20 OS, a complete regression of the inflammation in the anterior chamber and the vitreous, a progressive normalization of the fundus abnormalities (Figure 2), and no recurrence of the ocular condition when steroid therapy was tapered off. An adjunctive treatment of the IgG deficiency was begun using monthly infusion of 400 mg/kg of intravenous immunoglobulins. During a 2-year follow-up, no relapse of ocular inflammation was observed and her general situation improved. Repeated measurement of immunoglobulin levels during the 2-year follow-up revealed normalization of immunoglobulin G subclasses values.

DISCUSSION

IgG subclass deficiency is a frequent cause of primary immunodeficiency, characterized by recurrent infections and increased incidence of autoimmunity disorders, such as cerebral vasculitis, Henoch-Schonlein purpura, immune thrombocytopenic purpura, hemolytic anemia, and intractable epilepsy during childhood.[1,2] Autoimmunity occurs in 12.5% of overall IgG subclass deficiencies[3] and its pathogenesis remains largely debated. While it has been reported that abnormalities of humoral regulation could explain autoimmune manifestations in IgG subclass deficiency,[1,3] how autoantibodies can trigger internal tissues in a state of impaired antibody production is unclear.

IgG subclass deficiency associated with cerebral vasculitis has already been reported,[1,2,4] but its association with retinal vasculitis has not been described to date. To the best of our knowledge, we report here the first observation of retinal vasculitis revealing IgG subclass deficiency.

Retinal vasculitis is an inflammatory disease of the blood vessels of the retina that may be associated with primary ocular conditions or with localized or systemic inflammatory or infectious diseases.[5] The most common systemic diseases associated with retinal vasculitis are Behçet disease, sarcoidosis, and multiple sclerosis. Associations have also been noted with Wegener granulomatosis, systemic lupus erythematosus, polyarteritis nodosa, and other rheumatologic conditions. Infectious agents may produce a retinal vasculitis, including bacteria (e.g., syphilis or tuberculosis), viruses (mostly *Herpesviridae*), and parasites (including *Toxocara canis*). Primary ocular causes of retinal vasculitis include Eales disease, pars planitis, birdshot retinochoroidopathy, and some cases of Fuchs uveitis syndrome.[5]

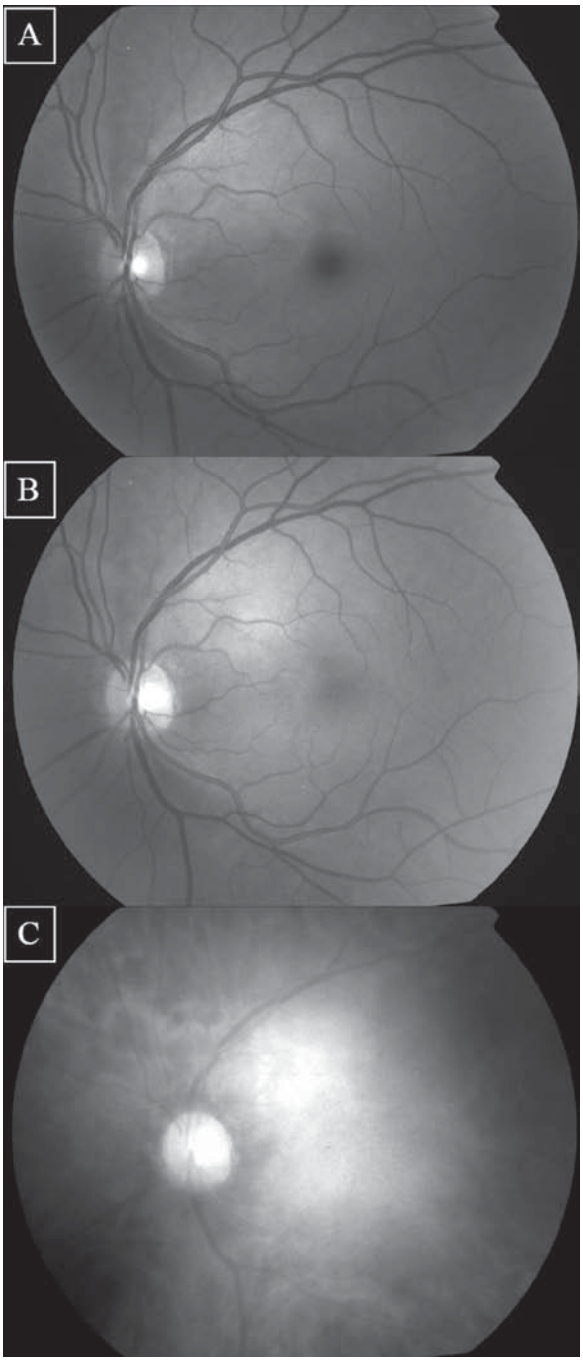

FIGURE 2 Monochromatic fundus photography after treatment. Normalization of the fundus abnormalities.

In our case, other etiologies of retinal vasculitis, including infectious and inflammatory causes, have been ruled out. No evidence of any infection was present either in the eye or systemically. However, deficiency of IgG subclass may induce false-negative serologies,[6] and then could decrease the diagnostic power of serological assays. In our observation, the patient had a history of ZVZ recurrent episodes, which could be explained by the central role of immunity in the control of subclinical episodes of VZV reactivation in the neurological sites of latency.[7] Direct diagnosis for other active infection with HIV, CMV, or EBV was negative. Additionally, the patient had persistent diarrhea, which is one of the most prevalent manifestations of IgG subclass deficiencies.[2,3] Prior to the ocular episode, this bowel disease had been explored, resulting in a diagnosis of pseudo-Crohn disease, due to the presence of bowel inflammation without a definite histological aspect and with no improvement of diarrhea by anti-inflammatory drugs.

Systemic steroids are generally efficient on autoimmune retinal vasculitis,[1,8,9] and this was the case in our patient since hyalitis and vasculitis improved rapidly after the onset of oral prednisolone. Additionally, the onset of monthly perfusions of immunoglobulins resulted in an improvement of the general conditions and the lack of ocular relapses during a 2-year follow-up.

CONCLUSION

IgG subclasses deficiency is a possible etiology of apparently isolated retinal vasculitis. This diagnosis should be evoked in patients presenting with retinal vasculitis with otherwise repeated infections, autoimmune disorders, and negative results of the usual uveitis workup.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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