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DAHİLİ BİLİMLERİ/ *MEDICAL SCIENCES*
Olgu Sunumu / Case Report

Central Retinal Vein Occlusion Following Intravenous Immunoglobulin Treatment in a Patient with Pemphigus Vulgaris

Intravenöz Immunoglobulin Tedavisi Sonrasi Santral Retinal Ven Oklüzyonu Gelişen Bir Pemfigus Vulgaris Hastası

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A 68-year-old male has been treated with prednisolone and intravenous immunoglobulin (IVIG) therapies with the diagnosis of pemphigus vulgaris. When he applied to receive the fifth session of IVIG therapy, he complained about visual loss. On the ophthalmologic examination, left central retinal vein occlusion (CRVO) was determined. There was no other detected underlying cause for CRVO and it was thought that central retinal vein thrombosis might be due to IVIG therapy.

IVIG treatment is generally accepted reliable for pemphigus vulgaris. However, it can rarely cause serious side effects like thrombosis. In literature, there are a few cases of central retinal vein occlusion due to IVIG therapy and none of these have dermatological disease as their etiology.

Key Words: ***Central Retinal Vein Occlusion, Intravenous Immunoglobulin, Pemphigus Vulgaris***

Pemfigus vulgaris tanısı almış olan 68 yaşındaki erkek hastaya prednizolon ve intravenöz immunoglobulin (IVIG) tedavisi uygulandı. Hastada 5. IVIG tedavi seansı sonrasında görme azlığı şikayeti gelişti. Oftalmolojik muayenede sol santral retinal ven oklüzyonu (SRVO) tanısı koyuldu. Hastada SRVO açıklayacak başka sebebin bulunamaması üzerine, IVIG tedavisinin santral retinal vende tromboza neden olabileceği düşünüldü.

IVIG tedavisi pemphigus vulgariste kabul gören bir tedavidir. Ancak nadir de olsa tromboz gibi istenmeyen ciddi yan etkilere sebep olabilir. Literatürde, IVIG tedavisine bağlı birkaç SRVO vakası tanımlanmakla beraber hiçbirinde etiyoloji dermatolojik bir hastalık değildir.

Anahtar Sözcükler: ***Santral Retinal Ven Oklüzyonu, Intravenöz Immunoglobulin, Pemfigus Vulgaris***

Pemphigus vulgaris is a life-threatening autoimmune bullous disease. Adjuvant treatments are needed because of serious side effects of traditional treatments such as high-dose, long-term systemic steroids or because of no response to treatment. Intravenous immunoglobulin treatment (IVIG) is generally accepted reliable. But it can cause rarely serious side effects like thrombosis (1). To our knowledge, there are a few central retinal vein occlusion (CRVO) cases in the literature due to IVIG treatment. We present a case of CRVO following intravenous immunoglobulin treatment for pemphigus vulgaris.

Case report

A 68-year-old male has been treated with prednisolone (onset dose was 120 mg/day) and azathiopurine (150 mg/day) with the diagnosis of pemphigus vulgaris one year ago. But, azathiopurine was stopped by the gastroenterology department because of the increase of the liver enzymes. The patient had pain and tremor on the legs and steroid myopathy was diagnosed by neurological examination. Also, after a short time, the patient started to complain about an intense back pain and multiple compression fractures were diagnosed by radiological examination. The patient was treated with stabilitation corset and bed rest. Because of complications related to the steroids, as an adjuvant therapy, we have initiated IVIG treatment, 400 mg/kg/day, with 5 days/month cycles after repeating laboratory tests and the actual steroid

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therapy has been decreased gradually. When the patient applied us to receive fifth session of IVIG, he has been taking 10 mg prednisolon every other day and had the complaint of visual loss at the left eye. This complaint occured 2 weeks after 4th session. On ophtalmological examination, the vision of left eye was 0.05, biomicroscopic findings were normal. Dilated fundus examination revealed dilated and tortuos retinal veins with patchy retinal hemorrhages, a few cotton wool spots and optic disc edema (Figure 1). Intraocular pressure was normal and left CRVO diagnosis was made. Fundus fluorescein angiography and optical coherence tomography confirmed the diagnosis (Figure 2,3). On general physical examination, blood pressure was 130/80 mmHg and heart rate 72/min and rhytmic. Patient had no smoking, hypertension, cardiovascular disease history. The tests for complete blood count, erythrocyte sedimentation rate (ESR), serum glucose level, hepatic, renal and thyroid functions, lipid profile, blood coagulation profile, antinuclear antikor (ANA), protein C and S activities, lupus anticoagulant, anticardiolipin antibodies, serum protein and immune electrophoresis, homocystein level were all in normal limits. Also, chest radiography, ecocardiography, abdominal ultrasonography and carotid doppler ultrasonography examination revealed no pathology. It was thought that central retinal ven thrombosis might be due to intravenous immunoglobulin therapy. Intravitreal dexamethasone implant was applied by ophthalmology department and the patient was taken under a follow-up period. Because the patient has been still in remission for pemphigus vulgaris about 8 months with IVIG and low-dose systemic steroid and has no other predisposing factor for thrombosis, IVIG therapy has been continued by the permission of ophthalmology department. 5th application was made 1 month after the intravitreal dexamethasone implant therapy and no other IVIG related complication including thrombosis was determined for 10 months follow-up. Pemphigus vulgaris lesions of the patient is in remission and IVIG therapy has been already administered with 8 weekly periods.

Figure 1: Fundus photography of the left eye showing central retinal vein occlusion with hemorrhages and cotton-wool spots

Figure 2: Fundus fluorescein angiography of the left eye with non-ischemic central retinal vein occlusion

Discussion

IVIG is a concentrated human Intravenous immunoglobulin treatment obtained from the donor plasma. The mechanism of effect is not well-known. It is considered to have an immunomodulator role in the autoimmune bullous diseases like pemphigus vulgaris (2). Although considered safe, even in high dose, IVIG can cause thromboembolic events such as stroke, myocardial infarctus, deep vein thrombosis and/or pulmonary thrombosis, peripheral arterial occlusion, spinal arterial occlusion and retinal infarct, superficial vein thrombosis, central retinal vein thrombosis and transvers sinus vein thrombosis (2-6). To date, as far as we know, there are 5 cases in the literature that CRVO is developed with IVIG treatment and none of these cases have dermatological disease (2-6). Table 1 shows the summary of these cases.

We think that thrombosis is related with IVIG treatment because he has been taking steroid treatment more than one year and CRVO developed while the patient was having steroid dose as low as 10 mg, every other day. Also, the patient has no thrombosis causing pathologies such as hypertension, hyperlipidemia, coronary artery disease. He has no smoking history. And no diseases related to CRVO such as hypergamaglobulinemia, cyrioglobulinemia and hyperhomocysteinemia are obtained by the laboratory tests. In our case, three weeks after the fourth administration of IVIG visual loss developed, this period was consistent with the literature.

The mechanism of thrombosis due to IVIG treatment is not well understood. One of the possible mechanisms is the increase in viscosity which is dose-dependent and related to duration of treatment (7). Also it is proposed that IVIG treatment can cause thrombotic occlusions by causing changes in the profiles of cytokine and vasoactive subtances. Human immunoglobulins with dose dependent mechanisms can cause a decrease in nitric oxide production which is triggered by thrombin. Nitric oxide prevents thrombosit aggregation and play an important role in vascular hemostasis by making vasodilatation (8). Furthermore in-vivo studies have shown correlation between IVIG adverse reactions and elevated levels of IL-6, a proinflammatory cytokine, and thromboxane, a vasoactive substance (9). Suchlike alterations in the profile of cytokines and vasoactive substances may have triggered the thrombotic adverse reaction.

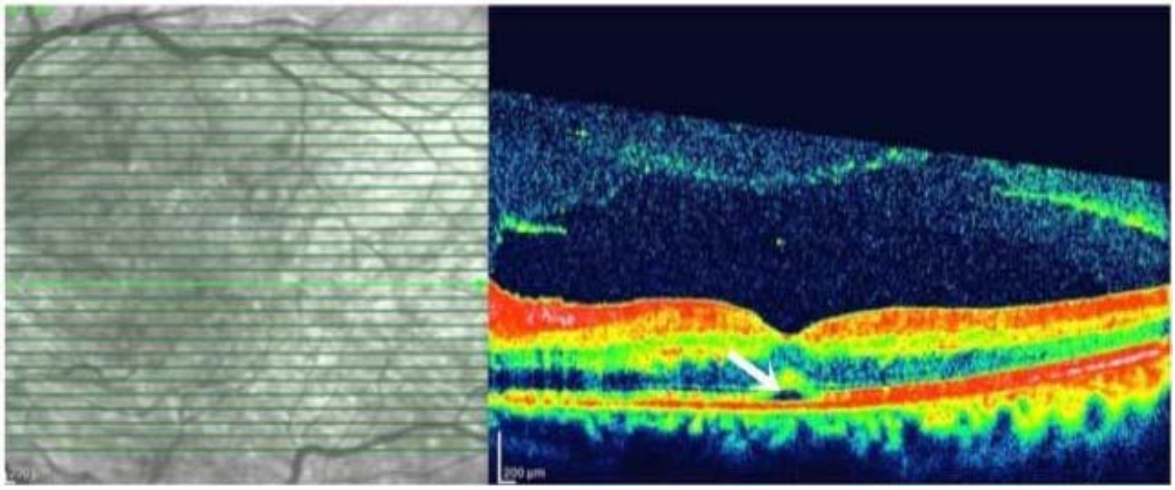

Figure 3: Optical coherence tomography revealed minimal subfoveal fluid collection.

Table 1: Summary of the IVIG related CRVT cases in the literature

	Age, sex	Diagnose for IVIG used	IVIG dosage	Time for CRVO occured	Precipitating comorbidity/risk factor	Concomitant medications	Viscosity
Case 1	17, male	Acute lymphoblastic leukemia in remission for 7 months	500mg/kg/day for 14 days	2 weeks after starting IVIG	High IgG level (4,96g/dl) and total protein level (10.9g/dl)	Ganciclovir, foscarnet, cyclosporine,norfloxacin, cotrimazole, metocloropramide,atenolol, and loperamide.	High (2.1)(Normal values<1.70)
Case 2	40, female	Chronic inflammatory demyelinating polyneuropathy	400mg/kg/day, for 5 days, monthly	3 weeks after the third day case administiration	Raised cholesterol	High dose oral prednisolone and azathioprine	Normal (1.64)
Case 3	57, male	Multifocal motor neuropathy	1g/kg/day, for 2 days, every five weeks	5 days after the fourth session	Hypertension under control	Losartan potassium-hydrochlorothiazide 50/12.5	----
Case 4	27, female	Guillain Barré syndrome	400mg/kg/day, for 5 days, monthly	14 days after starting IVIG	---	---	---
Case 5	31, male	Cystic fibrosis	400mg/kg/day, for 5 days, monthly	9 months after starting IVIG	Hypertension under control, high triglycerid levels, hyper homocysteinemia hyper gamma globulinemia and cryoglobulinemia	----	----
Present case	68, male	Pemphigus vulgaris	400 mg/kg/day, for 5 days, monthly	After fourth session	----	Low dose oral prednisolon	-----

Some risk factors such as raised cholesterol and triglycerid levels, hyperhomocysteinemia, hypertension, hypergamaglobulinemia, crioglobulinemia and high total protein level have been reported in the cases of CRVO due to IVIG therapy (3-5). Our case did not have any predisposing pathology for CRVO but exposure of long term corticosteroid therapy may be a facilitator for development of IVIG induced CRVO in our patient.

We aimed to draw attention to thromboembolic side effects of IVIG treatment with this case report. Especially in patients who have to use high dose systemic steroids, as in pemphigus vulgaris, thromboembolic complications must be kept in mind during IVIG treatment. Also in patients who have pathologies that trigger thrombosis, more attention is needed before the treatment. Especially, the patients who have emerging eye symptoms during the treatment must be evaluated for the possibility of CRVO.

Learning points:

- Adjuvant treatments are needed for pemphigus vulgaris because of serious side effects of traditional treatments such as high-dose, long- term systemic steroids or because of no response to treatment.
- Intravenous immunoglobulin treatment is alternative therapy option generally accepted reliable.
- Hovewer, intravenous immunoglobulin treatment can cause rarely serious side effects like thrombosis.
- Central retinal vein occlusion due to intravenous immunoglobulin treatment is extremely rare.
- Especially, the patients who have emerging eye symptoms during the treatment must be evaluated for the possibility of central retinal vein occlusion

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