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Abstract

A 41-year-old man was referred with a complaint of visual loss in his left eye and his best corrected visual acuity was 20/80. Slit lamp examination showed arborizing conjunctival vessels and dry eye. Fundus examination and fluorescein angiography revealed a non-ischemic central retinal vein occlusion. Cardiovascular, rheumatologic, and hematologic work up showed no abnormal findings. An ascertained history of exposure to sulfur mustard during the Iran-Iraq war was documented in his medical history. Four sessions of intravitreal bevacizumab injections were done as needed. After two-year follow-up, visual acuity in his left eye improved to 20/25 and macular edema was resolved without any need for further interventions. We conclude that sulfur mustard gas exposure may be considered as a predisposing factor for central retinal vein occlusion, as was found in our patient (an Iranian war veteran) by excluding all yet known etiologies and predisposing factors.

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Keywords • Sulfur mustard • Central retinal vein occlusion • Retina • Visual loss • Iran

Introduction

Chemical warfare agents (CWA) such as sulfur mustard (SM), a vesicant agent, were extensively used against the Iranian troops and civilians during 1983-1988.1 Initial toxic effects of SM involve the lungs, skin, and eyes. Moreover, proliferating cells of bone marrow may also be affected. Other proliferating stem cells may also involve and induce long-term impairments, including respiratory and ocular complications.2-8

Central retinal vein occlusion (CRVO) is a relatively common retinal vascular disorder and a frequent cause of visual morbidity in patients older than 50 years and can be associated with systemic vascular disease and coagulopathy. Although most patients with CRVO are over 65 years, it can occur in younger patients commonly termed papillophlebitis. Younger patients frequently have an associated inflammatory cause or coagulopathy, which deserve particular attention.9

Up to now, as far as we are aware, no early or late retinal complication of SM exposure has been reported. Here, we report a fairly young man presented with non-ischemic CRVO without any systemic known predisposing factor except for a history of SM exposure.
A 41-year-old man was referred to our eye hospital with a complaint of sudden visual loss in his left eye. An eye examination showed that his best corrected visual acuity (BCVA) in the right eye (RE) was 20/20 and in the left eye (LE) was 20/80. Relative afferent pupillary defect (RAPD) was slightly positive in the left eye as sluggish movement of the iris. Intraocular pressure (IOP) was 13 and 15 mmHg in RE and LE, respectively. Slit lamp examination showed arborizing conjunctival vessels and dryness in both eyes. Tear break-up time was less than five seconds, which indicated an abnormal tear film. Funduscopic examination of his right eye showed no specific abnormality. In the left eye, retinal hemorrhage in all quadrants of the retina, retinal edema, venous tortuosity, and macular edema were present (Figure 1). In fluorescein angiography delayed circulation, hyperfluorescence due to the breakdown of the blood-retinal barrier, venous tortuosity, and blockage due to retinal hemorrhages were obvious (Figure 2). In ocular optical coherence tomography (OCT), macular edema was obvious and central macular thickness was increased to 357 microns (Figure 3). The findings were compatible with a diagnosis of non-ischemic CRVO.

Systemic workup and initial laboratory tests for known causes of CRVO were performed. Purified protein derivative (PPD) test was negative (4 millimeters). HIV (ELIZA), antinuclear antibody (ANA), and rheumatoid factor (RF) tests were also negative. Chest X-ray was normal. All biochemical, immunological and hematologic investigations revealed no abnormalities and the results are summarized in Tables 1 and 2.

The patient had no history of systemic arterial hypertension, no obvious cardiac disease, and no connective tissue diseases. However, cardiology and rheumatology consultations were requested. Echocardiographies, both transthoracic and trans-esophageal, were negative for structural cardiac abnormalities. Carotid Doppler ultrasonography results were within normal limits. Rheumatology consultation also revealed no related connective tissue disease. Although all routine coagulation laboratory tests were within normal limits, we also requested hematologic consultation to rule out any coagulopathies. The result was normal. After 15 months, the consultations were repeated and again all were reported as normal.

Again, we reviewed his possible use of any drug, medication (either chemical or herbal) trauma, smoking, and familial history of such diseases. They were all negative. However, the patient had three times exposure to SM during 1987-1988 Iran-Iraq war. He had ambulatory admission and treatment in a field hospital after
the last SM exposure in 1988 and recovered within two days. Since then, he has never had any serious complication.

Following written informed consent, he received four serial intravitreal injections of an anti-vascular endothelial growth factor, bevacizumab (1.25 mg/0.05 milliliter), as an off-label treatment modality. After one year, the central macular thickness decreased to 334 microns and vision improved to 20/25. No obvious systemic or ocular complications related to the injection were noticed. The patient was followed up for more than 24 months during which he had stable retina and vision. IOP did not increase more than 20 mmHg during the follow up period. The patient was informed about the publication of this case report and an oral consent was obtained.

**Discussion**

Sulfur mustard (SM) [bis-(2-chloroethyl) sulfide] is an oily liquid. SM and similar bifunctional agents have been produced as chemical weapons since the 19th century. High dose exposure to SM may result in death within hours or weeks. However, low-dose exposure may cause injury to the eyes, skin, and respiratory tract without any mortality. Very low dose of SM exposure may not induce any symptom or sign and thus it is called subclinical exposure. It seems that our patient had two subclinical exposures in 1987 and one mild symptomatic SM exposure in 1988, after which he recovered within a couple of days. However, long term effects and delayed complications of SM poisoning are well known and several reports are available, particularly on the respiratory tract without any mortality. Very low dose of SM exposure may not induce any symptom or sign and thus it is called subclinical exposure.

The eye is the most sensitive organ to SM. It could be due to ocular characteristics such as high turnover rate, intense metabolic activity of corneal epithelial cells, and the aqueous-mucous surface of the cornea and conjunctiva. As it is absorbed by the lungs and skin, it may disseminate in the body and act as a toxic agent involving the internal organs as well. To our knowledge, no retinal abnormal finding ensuing SM exposure has been reported yet. Endothelial cells are proposed to be injured in the SM toxicities and may induce apoptosis and necrosis in endothelial cells all over the body. This may explain the vascular permeability in acute phase after exposure, which can result in bronchial edema. Long term effect of SM on vessels may predispose them to occlusion, particularly in microvasculature system such as the retina. This may explain possible mechanism of retinal vein occlusion in our patient.

CRVO is usually associated with systemic cardiovascular diseases and coagulopathies; and is mostly observed in elderlies. However, it is difficult to find the etiology of CRVO in youth.

| Test                          | Result | Unit       | Normal       |
|-------------------------------|--------|------------|--------------|
| Antithrombin III              | 115    | %          | 80-125       |
| Factor V leiden               | 3.3    | Ratio      | More than 2  |
| Serum protein electrophoresis | 59.66  | %          | 52-63        |
| Albumin                       | 1.64   | %          | 1.5-4.5      |
| Alpha 2                       | 9.75   | %          | 6-12         |
| Beta                          | 13.46  | %          | 11-17        |
| Gamma                         | 14.67  | %          | 11-19        |
| Complete blood count          |        |            |              |
| White blood cell              | 6500   | Cell/microL | 4500-11000   |
| Neutrophil                    | 3600   | Cell/microL | 2000-7500    |
| Lymphocyte                    | 2100   | Cell/microL | 1500-3500    |
| Red blood cell                | 5.14×10^6 | cell/microL | 4.5-6 |
| Hematocrit                    | 46.0   | %          | 42-48        |
| Platelet                      | 178×10^2 | cell/microL | 100-450     |
| C reactive protein (CRP)      | 1      | Mg/l       | 0-5          |

| Test                          | Result | Unit       | Normal       |
|-------------------------------|--------|------------|--------------|
| Serum protein C               | 88     | %          | 70-150%      |
| Serum protein S               | 124    | %          | 65-135%      |
| Protein C activity            | 140    | %          | 70-160%      |
| Protein S activity            | 131    | %          | 55-160%      |
| Anticardiolipin (IgM)         | 1      | Mpl/ml     | Up to 12     |
| Anticardiolipin (IgG)         | 2      | Gpl/ml     | Up to 12     |
| Anti-phospholipid Antibody    | 2      | IU/ml      | Up to 15     |
| Anti-Phospholipid antibody (IgG) | 1 | IU/ml | Up to 12 |
| Prothrombin time (PT)         | 13     | Seconds    | 13           |
| Partial thromboplastin time    | 29     | Seconds    | 30           |
| Fasting blood sugar           | 92     | Mg/dl      | 70-100       |
| Cholesterol                   | 163    | Mg/dl      | 120-200      |
| Triglyceride                  | 46     | Mg/dl      | 40-200       |
| LDL-C                         | 39     | Mg/dl      | 30-80        |
| HDL-C                         | 88     | Mg/dl      | Up to 160    |
| Creatinine                    | 0.9    | Mg/dl      | Up to 1.2    |
| Homocysteine                  | 13.4   | Micromol/l | 5-15         |

| Test                          | Result | Unit       | Normal       |
|-------------------------------|--------|------------|--------------|
| Protein C                     | 88     | %          | 70-150%      |
| Protein S                     | 124    | %          | 65-135%      |
| Albumin                       | 59.66  | %          | 52-63        |
| Alpha 1                       | 1.64   | %          | 1.5-4.5      |
| Alpha 2                       | 9.75   | %          | 6-12         |
| Beta                          | 13.46  | %          | 11-17        |
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**Table 1:** Results of the biochemical and immunological investigations

**Table 2:** Results of the hematologic investigations

Sulfur mustard exposure and CRVO
It has been evident that CRVO is different in young adults from older patients. CRVO in young adults is probably a general (nonspecific) change that results from a number of individual causes or a combination of causes. In unusual cases, the cause is known but in the vast majority of the patients, the specific cause or even the contributing factors are unknown. This is mainly due to limited literature and the paucity of histopathologic material from patients with such condition.\(^{11}\)

In our case, we performed a wide array of laboratory tests, systemic work up, and consultations according to the current findings and algorithms.\(^{10,11}\)

As all our tests and consultations were normal, we re-evaluated the patient and found a history of exposure to SM, a highly toxic chemical warfare agent that may have caused or played a predisposing factor for his non-ischemic CRVO. We thus propose that SM may cause or act as a predisposing factor for non-ischemic CRVO. However, experimental and clinical studies are required to confirm this hypothesis.

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**Conflict of Interest:** None declared.

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