Case of Sympathetic Ophthalmia

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Case Presentation:

The patient is a 61 year old female whose left eye was lacerated from a motor vehicle accident in 1975, which was repaired and resulted in light perception vision. However, 3 months later she developed sympathetic ophthalmia. The left eye was enucleated. Histopathology revealed a diffuse choroidal granulomatous inflammation. The choriocapillaris were spared. Focal areas of RPE proliferation were found, suggestive of Dalen-Fuchs nodules. The patient was treated with oral prednisone for 2 years. In 1987 the patient developed recurrent uveitis, which was treated with prednisone until 1989. Since April 1993, the granulomatous iritis, with no posterior uveitis. She then developed diabetes mellitus, and complained of muscle aches. She was examined by a rheumatologist and a neurologist, but no conclusive diagnosis was made. Her neurologist attributed her symptoms to diabetic peripheral neuropathy. A workup at this time, including rheumatoid factor, ANA, erythrocyte sedimentation rate, ACE X-ray was negative. The patient was referred in November 1994. On examination, the vision in the remaining right eye was 20/25. The right eye had mild episcleritis, but no signs of active iritis. The cornea was clear, the iris and lens were unremarkable. Trace cells were noted in the vitreous. The fundus exam showed diffuse granularity of the RPE (Fig. 1). Methotrexate was started in January 1995, and prednisone was tapered.

Discussion:

Sympathetic ophthalmia is a bilateral granulomatous uveitis that occurs after a penetrating injury to one eye. Although it is a potentially blinding disease that involves both eyes. The concept of injury to one eye resulting in damage to the other eye can be traced to the writings of Hippocrates. The earliest clear reference is that by George Bartisch, who wrote that after injury the eye may shrink and become painful, "in this case the other eye is in great danger." William Mackenzie first gave the complete description of the disease in 1840. Fuchs was the first to describe the histopathology of this entity.

Regarding the incidence of the disease, the literature is filled with dubious data. Often the diagnosis is presumptive. Sympathetic ophthalmia occurs more frequently now following nonsurgical trauma. Liddy and Stuart reported an incidence of 0.5% of nonsurgical injuries. Marak estimated the incidence to be less than 0.01% following surgical procedures. Sympathetic ophthalmia is more common in men, as a result of higher incidence of ocular trauma. An association between HLA-A11 and sympathetic ophthalmia has been suggested. Phacoanaphylaxis is reported to occur in 23 to 46% of eyes with sympathetic ophthalmia (7,8). It is thought that the patients with both entities occurring in the same eye have a predisposition for melanoma has also been associated with sympathetic ophthalmia. In a study of 400 cases of sympathetic ophthalmia...
Pathology, 7 were found to have malignant melanoma (9). In addition, sympathetic ophthalmia was reported to occur after cyclocryotherapy (11) and Nd:Yag cyclotherapy. Nd:YAG cyclotherapy in particular, is associated with a much higher incidence compared with other ocular procedures. A study from University of Illinois showed an incidence of 5.8% after noncontact cyclotherapy performed at that institution (12).

The onset of sympathetic ophthalmia is usually between 2 weeks and 3 months following an ocular injury, although it can develop as early as several days and as late as 50 years. About 80% of cases present within the first 3 months. Classically the inflammation is granulomatous with muttonfat KP’s on the corneal endothelium. The anterior chamber reaction can be relatively mild, and the inflammation can be non-granulomatous; the term "sympathetic irritation" is used. There is usually a moderate to severe vitritis. Dalen-Fuchs nodules can be seen in the periphery. (Fig. 2) Papillitis can be prominent, and may be accompanied by peri-papillary choroidal lesions. Retinal involvement can be found, although the disease is classically thought of as a choroidal one. Subretinal neovascularization may occur.

Extraocular findings such as pleocytosis in the cerebrospinal fluid, hearing disturbances, alopecia, poliosis, and vitiligo are rare in sympathetic ophthalmia when compared with VKH. During the acute phase of the disease, fluorescein angiogram shows multiple subretinal hyperfluorescent spots, which correspond to the clinically observed Dalen-Fuchs nodules. Less commonly, hypofluorescent spots are seen with late staining, similar to angio graphically observed posterior multifocal placoid pigment epitheliopathy. During the late cicatricial phase of the disease, the areas become atrophic, and appear on the angiogram as window defects. (Fig. 3) The sequelae of the inflammation include secondary glaucoma and cataract, retinal and optic nerve atrophy, retinal choroidal atrophy. (Fig 4)
Histopathologically, a diffuse granulomatous, non-necrotizing inflammation is seen throughout the uveal tract. The infiltration of lymphocytes. (Fig. 5) The infiltrates can also have large numbers of eosinophils, and sometimes plasma cells. Although this is not always the case. In addition, retinal detachment and retinal perivasculitis are often present. Dalen-Fuchs nodules are typical, but not pathognomonic findings of sympathetic ophthalmia. They are thought by Fuchs to represent migrated and transformed RPE cells. Jakobiec and Chan demonstrated, by using monoclonal antibodies, that Dalen-Fuchs nodules are composed of Ia+, OKM1+ cells, which OKM1- cells, which are depigmented RPE cells (13,14). (Fig. 6)
Jakobiec and colleagues also noted that the predominant infiltrating T cells were the CD8 subset (13). Chan and colleagues examined an eye enucleated only several months after the initial trauma and found the predominant T cells were the CD4 subset. However, when late infiltrating T cells changed to the CD8 subset (14). Therefore it appears that as the disease progresses, there is a change in the cellular immune response.

Although sympathetic ophthalmia is thought to be a T cell mediated disease, there was a study that reported 4 of 29 eyes of sympathetic ophthalmia with a predominant B cell infiltrate (15).

Histologically, compared to VKH, classic sympathetic ophthalmia is characterized by sparing of the choriocapillaris; this may be the result of the eyes being enucleated early in the course of sympathetic ophthalmia; in contrast, eyes course of inflammation.

The concept that an autoimmune reaction against retinal antigens, triggered by exposure of intraocular antigens, as has long been entertained. Lymphocytes from patients with sympathetic ophthalmia were demonstrated to respond no circulating antiretinal S-antigen antibodies were found, the serum from patients with sympathetic ophthalmia show the outer segments of the photoreceptors and the Muller cells, when placed over normal human retinal tissue (16). S detects in normal human retina, are found on the retinal Muller cells of eyes with sympathetic ophthalmia (17). The evidence that retinal Muller cells may have an immunoactive role.

The closest animal model for sympathetic ophthalmia is the uveitis induced by immunization with the ocular antigen: mice. The induced uveitis has many features of sympathetic ophthalmia, including Dalen-Fuchs nodules, and like sympathetic ophthalmia primarily involves the choroid.
A hypothesis of the pathogenesis of the disease is that the perforating wound leads to the drainage of ocular antigen occur under normal circumstances. The injury may also allow adjuvants such as bacterial endotoxin to enter the eye inflammatory response to the degree to bypass certain suppressor mechanisms. Kupner et al studied samples from iris, ciliary body, choroid and retina from normal eyes and from eyes with acute and found the expressions of VLA-4, VLA-5, VCAM-1, ICAM-1 and CD44 were significantly increased in acute sym pathetic normal eyes; VLA-6 was moderately increased in both acute and fibrotic cases of sympathetic uveitis (18). Furt molecules in the pathogenesis of the disease may lead to immunotherapies with adhesion molecules as the specific Enucleation of the injured eye before the onset of inflammation in the sympathizing eye is the only way to prevent sympathetic ophthal mia indicated that enucleation within 2 weeks of the onset of the inflammation may lead to a more benign course and be eye (19,20). However, when the exciting eye still has useful vision, early enucleation can not be recommended, bec with more superior vision.

Medical treatment should begin with corticosteroids. Prednisone 1-1.5 mg /kg is given for 3 months, followed by a sl on 15-20 mg of prednisone for up to a year. In a study of patients treated with steroids, 65% of eyes were 20/60 or t 21

Other immunosuppressing drugs used in the treatment of this disease include methotrexate, cyclosporine, chloramph: Nussenblat and colleagues reported good results in 5 patients treated with cyclosporine (220. Tessler and colleague patients treated with short-term high dose chlorambucil (23). Ishioka and colleagues treated one patient with FK506. Finally of interest, sympathetic response in other organs such as the testis, has been observed. The disease occurs cord (25). It has been shown that the ischemic testis releases a factor into the blood stream that is cytotoxic to norm this factor can be prevented by the administration of steroids. It has also been suggested that auto-antigens release immunologic response which involves the contralateral testis, accounting for the pathologic changes.

References:

10. Margo CE, Pautler SE. Granulomatous uveitis after treatment of a choroidal melanoma with proton-beam irradiation

**Review Questions for Sympathetic Ophthalmia**

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1. Which of the following statements is false:
   a. the incidence of sympathetic ophthalmia is higher following ocular trauma than ocular surgery.
   b. the incidence of sympathetic ophthalmia is higher in men.
   c. sympathetic ophthalmia develops only after penetrating ocular injury or surgery.
   d. HLA-A11 is associated with sympathetic ophthalmia.

2. All of the following are associated with sympathetic ophthalmia except:
   a. phacoanaphylaxis
   b. malignant uveal melanoma
   c. intraocular lymphoma
   d. cyclocryotherapy

3. Which of the following is false regarding sympathetic ophthalmia:
   a. Mutton fat KP’s can be present.
   b. If the inflammatory response is nongranulomatous, the diagnosis of sympathetic ophthalmia should be doubted.
   c. Extraocular findings such as hearing disturbances, hair and skin changes can occur.
   d. Retinal involvement can be found, although classically sympathetic ophthalmia is a choroidal disease.

4. Which of the following statements regarding Dalen-Fuchs nodules is false:
   a. They are typical, but not pathognomonic of sympathetic ophthalmia.
   b. On fluorescein angiogram, they may block early and stain late.
   c. On fluorescein angiogram, they may appear as window defects.
   d. They are shown to be composed of depigmented RPE cells and lymphocytes.

5. All of the following statements are correct except:
a. Sympathetic ophthalmia may represent an autoimmune inflammatory response.
b. Circulating antiretinal S-antigen antibodies are present in patients with sympathetic ophthalmia.
c. Lymphocytes from patients with sympathetic ophthalmia were shown to respond to several autoantigens.
d. The expression of certain adhesion molecules is significantly increased in eyes with sympathetic ophthalmia.

6. (True / False) Once sympathetic ophthalmia develops, enucleation of the injured eye does not alter the course of the disease.

7. (True / False) Medical treatment of sympathetic ophthalmia with corticosteroids is often effective, with more than half eyes retaining useful vision.

ANSWERS:

1. c (references 10, 11, 12)
2. c (references 7, 8, 9, 11)
3. b (reference 5)
4. d (references 13, 14)
5. b (references 16, 18)
6. False (references 19, 20)
7. True (references 21)