

Uveitis and Glaucoma in Cowden Syndrome. Therapeutical challenge.

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Introduction

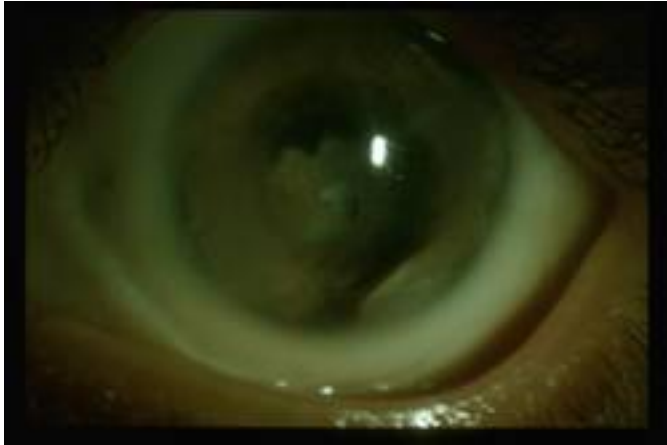
22-years old woman with recently diagnosed with Cowden Syndrome, was referred for recommendations regarding her glaucoma and uveitis treatment.

Case presentation

A Caucasian female, age 22, was referred for recommendations for treatment of uveitic glaucoma in her remaining right eye.

Her past ocular history was significant for bilateral uveitis at age 4, complicated by retinal detachment OS and OS phthisis. Her right eye needed surgical excision of a vitreo-retinal traction band. After a period of stability, retinal detachment developed in the right eye and was successfully treated with pars plana vitrectomy and scleral buckling at age 13 years. Secondary cataract developed, requiring cataract extraction. Best-corrected vision at age 14 was 20/40. The intraocular pressure was normal until age 17. Glaucoma then developed, and the pressure was around 29 mmHg, despite therapy with dorzolamide, timolol, brimodine and latanaprost. The review of system was significant for status post pneumonia at age 16 and status post thyroidectomy two years earlier and recent diagnosis of Cowden Syndrome.

At the time of consultation with us, the patients best-corrected vision in OD was 20/30, pinhole 20/25; OS no light perception. The intraocular pressures were 19mmHg OD and 6mmHg OS. Slit-lamp biomicroscopy OD revealed mild peripheral band keratopathy OD, quiet anterior chamber, normal iris, aphakia. OS showed a extensive band keratopathy and retro-pupillary membrane.



Fundus examination OD showed a clear vitreous cavity. The disc OD had extensive peripapillary atrophy and was covered by a fibrotic membrane, not allowing any judgement of the cup/disc ratio. The macula was normal and the peripheral retina attached.

A visual field was obtained, and showed a large defect superotemporally.

Recommendation

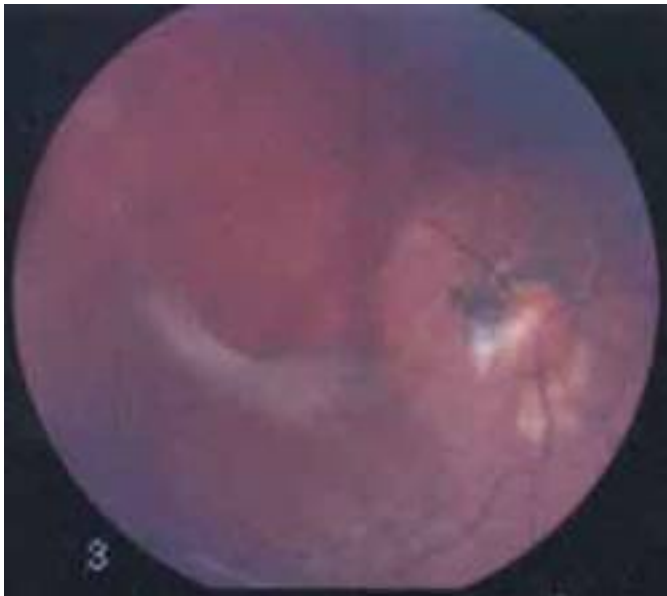
We recommended the implantation of an Ahmed valve OD with the intra-operative application of mitomycin C because of the history of uveitis and a systemic disorder known for keloid, excessive scar formation and uncontrolled connective tissue growth (Cowden Syndrome see below). Mitomycin C is an anti-metabolite and its intraoperative application during trabeculectomy may prevent scarring of the filtering bleb. Its use is limited as it carries some risks especially for endophthalmitis because of a possible entry of bacteria via the less scared filtering bleb. We felt that in this particular young woman any surgery performed would induce a hyper-proliferative reaction of the conjunctiva and sabotage the filtering surgery. In order to

counterbalance the known propensity of scarring associated with the systemic disorder; we recommended intraoperative application of mitomycin C and estimated the risk of endophthalmitis as small and acceptable.

Evolution

Molteno valve implantation was performed without the use of adjunctive mitomycin C. Post-operative high pressures could not be controlled conventionally; paracentesis for release of humor aqueous was performed multiple times. Eventually the pseudocystic filtering bleb was revised because of the high pressures. A period of transitional hypotony followed; the intraocular pressure rose, eventually, slowly and then rose to unacceptably high levels once more. Three pressure lowering eye-drops together with daily frequent digital massage were required to keep the intraocular pressure low and the shunt functioning.

At a second consultation, seven months after the first visit with us, the patient's visual acuity has fallen to 20/100. The intraocular pressure under therapy was 16mmHg; the anterior segment was quiet, the valve in place. Fundusscopic examination showed a thick fibrotic membrane in the inferior part of the macula, with traction on the fovea and distortion of the temporal retinal vessels.



Fundus photography of the right eye.

OCT shows a signal demonstrating the thickness of the membrane, a sharp edge and the traction on the retina below.

Further Recommendation

We recommended pars plana vitrectomy with membrane peeling and intra-operative instillation of both 5-fluorouracil and low molecular heparin in an effort to relieve the macular traction, reverse the macula edema, and improve vision. (Yusuf RH 2001)

Evolution

The surgery was performed successfully by Dr. Gary Abrams of the Kresge Eye Institute, Detroit, and visual acuity improved to 20/60 two weeks post-operatively. Intraocular pressure was 19mmHg.

Cowden Syndrome (CS)

Introduction

Cowden syndrome has also the name of “multiple hamartoma syndrome” and was first described by Lloyd and Dennis in 1963. It is part of the genodermatoses (skin condition of genetic origin), and it can be considered as part of other systemic hamartomatosis also known as phakomatosis such as neurofibromatosis of Recklinghausen, Tuberous sclerosis, Von-Hippel-Lindau disease, Sturge-Weber disease and Wyburn-Masen.

Hamartomas are by definition benign tumors or proliferation of mature cells or tissues occurring in places the cells or tissue are originally present as opposed to proliferation of cells or tissues in ectopic places, which are called choriostoma.

In Cowden Syndrome these hamartomas are present at various places such as the skin, and internal organs, and there is an association with malignancy (e.g. breast and thyroid). Up to forty percent of the patients develop one malignancy. Because of that, diagnosis of a patient with Cowden disease is important, and screening for malignancies is crucial in order to decrease the mortality and morbidity rate.

Pathophysiology

Cowden syndrome is a rare genetic disease with autosomal dominant transmission and variable expression. The gene defect is located on chromosome 10q23, a region called the PTEN gene, which is a tumor suppressor gene. The gene encodes a protein, which is an enzyme of the group of the protein phosphatase. Normally protein phosphatases are the natural antagonist of protein kinases.

Protein kinases/phosphatases have regulatory activities in metabolic and signaling pathways. The role of these enzymes is to modify the activation-state of other proteins by adding or removing phosphate groups on amino acid residues. Phosphates are negatively charged groups and by virtue of the attraction of positively charged amino acid residues in the protein induce a conformational change in the three-dimensional structure of the protein, thus liberating the biologically active site of the protein. Protein kinase function often as “ON” signal button whereas protein phosphatases split off these phosphate groups and inactivate the enzyme, effecting an “OFF” signal button.

PTEN phosphatase has an unusual broad spectrum of activity and specificity. Contrary to most phosphatases, the PTEN encodes an enzyme that recognizes and removes phosphate groups attached to three different amino acids. Furthermore, it is able to dephosphorylate phosphatidylinositol 3,4,5-trisphosphate, the product of the PI-3 kinase (phosphatidylinositol 3 kinase). This substrate is not a protein, but a lipid (=dual specificity).

It is specifically this last loss of function, which is thought to be responsible for the tumor-inducing effect. In tumor cells the concentration of phosphatidylinositol 3,4,5, trisphosphate is higher compared to normal.

Furthermore another protein kinase called protein kinase B is up-regulated by elevated 3,4,5,phosphatidylinositol triphosphate. Both phosphatidylinositol 3,4,5-trisphosphate and protein kinase B together are involved in the regulation of physiological cell death/apoptosis and specifically act to prevent or reduce apoptosis (see schema below). Since phosphatidylinositol 3,4,5 trisphosphate is not degraded and by intermediate of other molecules stimulating the protein kinase B, there is an “overpreservation” of cell life, inducing a disequilibrium between cell birth and cell death, resulting in overproliferation.

Since the “OFF” signaling button is defective, the system is over-activated resulting in hyperproliferation of cells. (simplification)

In Cowden Syndrome the PTEN defect is a germline defect, thus inherited and present in all cells, resulting in overproliferation of cells in various tissues.

PTEN mutations have been found in somatic mutations, thus inducing overproliferation of a specific, single tissue such as in glioblastoma, melanoma, prostate and endometrium cancers. The PTEN mutation alone is not sufficient to transform cells since the mutation exists in another syndrome clinically similar to Cowden disease, called Bannayan-Zonana Syndrome, which is generally not associated with malignancy.

Clinical picture

Women and men are equally affected (autosomal); age of onset from birth to 46 years.

Hamartomatous neoplasm of the skin and mucosa, GI tract, bone, central nervous system,

genitourinary tract, endo- and exocrine system.

Mucocutaneous features are present in 90-100% cases and include

- trichilemmoma (proliferation of the outer sheet of the root of the hair) especially at periorificial regions but also on eyelids,
- oral mucosal papillomatous growth,
- verrucoid papules on the dorsal hands or feet,
- palmoplantar keratoses,
- lipomas, neuromas, hemangiomas,
- keloids



Oral mucosal papillomatous growth on the tongue

Macrocephaly is present in 80% of the cases.

Lhermitte-Duclos disease is often associated, and caused by hamartomatous growth of the cerebellum. Patients present with slowly progressive cerebellar ataxia and signs of intracranial hypertension.

Thyroid lesions occur in 60% and manifest as

- goiter, benign adenoma, thyroglossal duct cyst and
- follicular adenocarcinoma. (men>women)

Breast lesions include

- Fibrocystic disease
- Fibroadenoma
- Carcinoma in 20-36% of female patients (2 case reports in men).

Others: GI Polyps (very frequent, but fortunately with low malignancy rate), ovarian cysts, leiomyomas, teratomas, adenocarcinoma of urethra, cervix, renal cell carcinoma, transitional carcinomas, bone cysts, osteosarcoma, etc.

Eye:

- myopia
- Angoid streak
- Cataract

Diagnostic criteria

The International Cowden Syndrome Consortium has proposed operational criteria.

Major criteria

Breast Cancer

Thyroid Cancer, especially follicular thyroid carcinoma

Macrocephaly (>97 percentile)

Lhermitte-Duclos disease

Minor Criteria

Other thyroid lesions (e.g. Adenoma, goiter and others)

GI hamartomas (polyps, most common in the colon)

Fibrocystic disease of the breast

Lipomas

Fibromas

Genito-urinary tumors or malformations

Operational diagnosis in a patient

Macrocephaly or Lhermitte-Duclos disease and one other major criterion

1 major and 3 minor criteria

4 minor criteria

Mucocutaneous lesions alone meet the criteria if patient presents

- 6 or more facial papules, 3 must be trichilemmomas (histo)

- cutaneous facial papules and oral mucosa papillomatosis

- oral mucosal papillomatosis and acral keratoses

- 6 or more palmo-plantar keratoses

Operational diagnosis in a patient in whose family one person is known for CD

- 1 major criterion

- 2 minor criteria

Differential diagnosis

Bannayan-Zonana Syndrome

Has identical mutation in PTEN, shares the same clinical features but has a much lower predisposition to cancer.

Trichilemmoma versus Trichiepithelioma

(Histology: large cells with clear cytoplasm opposed to horn cysts and basaloid epithelium)

MEN type III

(Multiple skin neuromas, pheochromocytoma, medullar carcinoma of thyroid)

Lipoid proteinosis

(Autosomal recessive transmitted disease with deposition of lipoid protein products, producing skin papules of faces, lids, neck and extremities)

Darriers disease (keratosis follicularis)

Management

Education of patient, teaching of self-screening techniques, annual physical exam with laboratory and other paraclinical investigations.

Discussion

Here at the Massachusetts Eye and Ear Infirmary we are confronted with a variety of patients with less frequent and rare conditions.

Obviously as Cowden disease is a very rare disorder, not every doctor consulted has a large clinical experience with the disease and the major issue is how to deal with the condition with no previous experience.

Reflections on the patients underlying pathology, the past ocular history and reactions either in the eye and elsewhere guide as we are trying to formulate a treatment plan.

Described in general terms, the knowledge of uncontrolled cell growth, present systemically as hamartomas, and of keloid formation in "stimulated" situations such as injury or surgery was important to us in formulating our recommendations. Together with the past ocular history of vitreoretinal traction band and the observation of a fibrotic membrane on the optic nerve led us to recommend aggressive strategies in order to counterbalance the expected over-reactive response produced by the patients disease.

The challenge to anticipate complications, and suggest more "creative" treatments makes this case an especially good example of the sorts of reflections we attempt in the care of patients with unusually difficult problems.

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Uveitis and Glaucoma in Cowden Syndrome.**Margherita E. Meniconi, M.D.**

1 Definition of hamartoma is

- a) proliferation of immature cells at a place they usually occur
- b) proliferation of immature cells at an ectopic place
- c) proliferation of mature cells at a place they usually occur
- d) proliferation of mature cells at an ectopic place

2 The clinical manifestation of genetic transmitted diseases is most severe

- a) in autosomal dominant transmitted diseases
- b) in autosomal recessive transmitted diseases
- c) in non-autosomal transmitted diseases

3 The onset of Cowden Syndrome

- a) can be at various ages
- b) is always at small ages
- c) is always at adulthood

4 Cowden Syndrome \rightarrow major diagnostic criteria include

Mark + or \rightarrow for each line

- a) Fibrocystic disease of the breast
- b) Carcinoma of the breast
- c) Head circumference on 95 percentile

d) Slowly progressive cerebellar ataxia

e) Goiter

f) Cancer of thyroid

5 Is Cowden disease usually diagnosed with a genetic test?

a) yes, because the gene involved is specific and pathognomic of the disease

b) no, because the gene involved is not pathognomic of the disease

c) no, because the test is too expensive and highly difficult to perform

Key:

1c,

2b,

3a,

4a-

4b+

4c-,

4d+

4e-

4f+

5b