



Medical Panel Questions and Answers

*Transcribed from audio recordings and edited
by Stephanie Angelovich, Intern*

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At the International Centennial Meeting on Pseudoxanthoma Elasticum, in November 1997, we had the good fortune to hear Charles Boyd, PhD, genetic researcher; Lionel Bercovitch, MD, dermatologist; Wayne Fuchs, MD, ophthalmologist, Mark Lebwohl, MD, dermatologist; and Jouni Uitto, MD, PhD, dermatologist. After their presentations, there followed a question and answer period. The questions were generated both by the assembled participants and by the readers of the MemberGram (sent in prior to the meeting).

The answers given here are a compilation of comments by the scientists on the various topics. This was an oral presentation and these comments are not 'polished', therefore. (All of the presentations, questions and answers are available on tape .)

Skin

Is dry, itchy skin related to PXE? Can soreness after scratching itchy skin be related to PXE? Could other symptoms, other than the usual lesions or bumps which are generally talked about, be a form of PXE? Are bumps on the knees cause for concern?

Dry, itchy skin is not specifically related to PXE, and skin-related diseases such as psoriasis and eczema are no more common in patients with PXE. This type of problem usually occurs due to a lack of hydration in the skin, and primarily affects the epidermis, the surface layer of the skin. Symptoms of PXE predominately affect the dermis, the deep dermis, and the elasticity of the skin. As far as bumps on the knees are concerned, if they resemble PXE, it is likely that they are PXE.

What may happen to the skin on the face, specifically the eyelids and lip area?

Most of the changes which occur around the eyelids are related to the normal aging process, or prolonged exposure to the sun. The eyelids are not usually a site in which PXE manifests itself. Many patients mistake PXE for a condition which can occur on the eyelids known as syringomas. These are enlarged sweat glands under the eyelids which give a yellowish color to eyelid skin. To date there has not been a documented case of PXE around the eyelid area.

Will PXE spread to my face?

One complication, prominent in patients with PXE, is lines around the jaw. These lines can occur in anyone as part of the aging process, however, in patients with PXE they

occur at an earlier age. Treatments are available, yet temporary, and far from perfection.

Vascular Complications

Do patients with PXE experience vascular complications?

PXE patients get calcifications of the lining inside the arteries because it is composed primarily of elastic tissue. During this calcification process arteries essentially become narrowed. Cholesterol, primarily involved in other conditions (especially heart related), is also a cause for concern in patients with PXE. In fact, the most common cause of intermittent claudication is atherosclerosis — the deposit of fats and cholesterol on the lining of the arteries. The wisest and safest course which patients should embrace is that of a heart-wise diet. This includes lower fat and cholesterol foods, and an exercise and lifestyle program to benefit the heart. Concern is turned towards the calcification of other arteries, primarily those surrounding the heart. A fair amount of research has been done at Mt. Sinai Hospital involving channel blockers. It has been found that these channel blockers have no negative impact, or beneficial impact, on PXE. If you suffer from high blood pressure it is perfectly fine to take calcium channel blockers; unfortunately, they will not make your PXE go away.

What causes vascular complications and are treatments available? Is cholesterol involved in the calcification process of intermittent claudication?

Intermittent claudication is like angina in the heart. For example, if you have a decreased blood supply, and you are exercising a muscle, you can develop what is called anaerobic metabolism which in turn causes an accumulation of metabolic substances within the muscle. The result is cramping and pain in the muscle. In severe cases, if your blood supply is greatly reduced, you can experience rest pain. This can occur when the legs are elevated and do not get enough blood supply due to gravity. Generally the claudication only occurs when the exercise is enough to outstrip the blood supply, and should not occur with simple tasks such as driving or sitting. There is a drug for intermittent claudication called Trental, which is safe for patients with PXE. It is typically used only in severe cases, and has very limited side effects.

Is foot pain and numbness due to vascular complication? And can this occur sitting as well as walking?

There are many symptoms which can occur when circulation in the legs is reduced. The pain can be not only in the calves, which is the most common site for PXE, but also in the feet. Pain can range from an aching feeling to the sensation of pins and needles, and also to a coldness, due to reduced blood flow.

Are angiograms more risky when performed on PXE patients?

Whether or not angiograms are more risky when performed on people with PXE is unknown. During an angiogram, a cut is made in the artery and a catheter with a balloon is inserted. The balloon is then inflated, a dye is injected, and X-rays are taken. As with any blockage, there is always a theoretical risk of knocking off little bits of cholesterol plaque, which can in turn form a clot and travel downward, blocking smaller vessels. Theoretically the same risk can occur with calcification through the wall of the artery, yet, in general, these are well recognized risks. Patients with PXE need not worry about being placed at a higher risk, however, it is essential to keep your physician informed about your existing condition.

Heart

What types of heart problems can occur in people with PXE? What are the chances of acquiring aortic valve stenosis with PXE? Can cardiac arrhythmia be a consequence of PXE?

The risk of acquiring aortic valve stenosis with PXE is very small, in fact it is a rare occurrence. The only common cause for cardiac arrhythmia in PXE is related to a valve change called mitral valve prolapse. More than two-thirds of PXE patients suffer from this condition. These patients complain of palpitations, which are very rapid heart beats. There are very easy benign treatments for this condition. Medications such as beta blockers are effective in reducing palpitations. Many patients, however, do not require the use of such drugs.

If a coronary artery bypass is performed what are the chances of new artery blockage?

There are a couple things which are important to know if a coronary bypass is performed. Unfortunately, arteries contain elastic tissue; therefore, first and foremost, the artery which is to be used needs to be biopsied to show if it is involved with PXE. If the artery proves to be involved, then the surgeon may opt for a venous bypass. However, a venous bypass may not last as long as arterial bypass. The chance of developing chest pain or symptoms of narrowing of the arteries after bypass surgery is not more likely in patients with PXE. Some will develop this, others will not. To date, the numbers of PXE patients who have undergone this procedure are relatively small and statistics are not available. The problems that can occur do relate to the narrowing of the arteries. Patients may develop a chest pain, diagnosed as angina (See intermittent claudication). This is usually precipitated by exertion, usually a pressure in the chest which can radiate down the shoulder or left arm.

There are actually very good predictive tests that doctors can perform. A stress test, an exercise tolerance test during which a cardiogram is taken while exercising. This can predict if you will experience complications in the future. The percentage of PXE

patients who develop narrowing of the arteries is very small, and as mentioned earlier, not that different from the normal population. As mutations are identified, it is possible that a group of patients who are predisposed to this condition will be found. There have been documented cases of teenagers who developed heart disease with PXE. A small number of patients have also been reported to have no skin lesions yet went on to develop a heart disease at a very early age. Hopefully, for most people with PXE, this will not develop.

Is exercise related to cardiac problems with PXE?

It is important to consult with a cardiologist who can give you advice on just how much to exercise and with whom you can form a routine. However as far as including exercise into your lifestyle, the answer is absolutely! Over time you should gradually increase your tolerance for exercise in order to reap benefits for many things, including PXE.

Would a very low HDL be a consequence of PXE?

HDL, which is a good type of cholesterol and protects against heart disease, is not increased in patients with PXE. Low HDL might be an additional risk factor for arterial blockage.

Gastrointestinal System

What types of surgical procedures are used to stop internal bleeding?

When discussing internal bleeding it is important to key in on two major aspects: 1) prevention, and 2) recognition. There is no question that some internal bleeding in PXE is due to the fact that the arteries have become calcified and are more prone to cracking or rupture. These arteries can bleed from multiple sites and this, in turn, becomes very difficult to identify and treat. Prevention is key. It is important to be aware that certain types of drugs make vessels more prone to bleed, causing ulceration and irritation, and therefore should be avoided. Drugs such as aspirin, non-steroidal anti-inflammatory drugs (specifically Ibuprofen, Naprosyn, Motrin, and Aleve), and some drugs used to treat arthritis should be avoided.

What kinds of tests are used to locate internal bleeding?

Recognition of symptoms is important as well. Gastrointestinal bleeding occurs high up in the intestinal tract and consequently does not come out the other end as bright red, but as black. The development of black tarry stools, or any kind of black discoloration of stools, (provided you are not taking iron supplements), is cause for concern. The test for the detection of occult bleeding, or bleeding which is not visible to the eye, is done with the use of a card called a Hemoccult slide. During this test a small amount of stool is smeared on the card and sent to a doctor's office. At the office a drop of developing

substance is placed on the card. If the card turns blue it is an indication of internal bleeding.

Once a diagnosis has been made confirming the presence of internal bleeding, the next step is to determine the cause of bleeding. Doctors use what is called a gastroscope and perform a procedure known as an endoscopy. In such a test, a fiber optic device with a television camera is threaded into the patient's esophagus and down into the stomach. This locates any bleeding points visible in the stomach. Many times, bleeding will stop with time and transfusions, and other times it may require surgical attempts to either oversee the bleeding vessel, if it is found, or embolize the vessel if it can be found on an angiogram. In PXE, because bleeding can be due to a ruptured artery, an arteriogram or angiogram may be required to actually find the vessel and see the leakage. A catheter can then be threaded to clot the vessel and stop it from bleeding, or surgery may be necessary if bleeding will not subside on its own.

Are surgical procedures available to relieve symptoms of abdominal angina? Is weight loss a consequence of abdominal angina? What are the symptoms of abdominal angina? What is the probability of acquiring abdominal angina with PXE?

Abdominal angina is a very uncommon disorder. Essentially it is intermittent claudication of the bowel. This can occur in people who have narrowing of the arteries that supply the intestinal tract with blood. This narrowing can cause cramping and diarrhea after meals due to lack of blood flow to the bowel. There are ways to treat abdominal angina. One way is by a radiology procedure in which the narrowed artery is located through an angiogram, and dilated by angioplasty. Attempts have also been made to surgically perform an angioplasty on affected arteries. If a patient suspects that he or she may have abdominal angina, they should notify their doctor who can do an angiogram to visualize the vessels and catheterize them to see if they have narrowed. Weight loss can occur as a result of abdominal angina if there is a high degree of malabsorption, however, this is rather uncommon.

Eye

What percentage of patients with PXE experience eyesight loss? Are there cases where patients have lost peripheral vision?

About 75% of patients with PXE, by their sixties and seventies, experience some type of visual impairment. PXE limits this loss to the center of the eye and therefore, if a patient was to lose peripheral vision, it would be from another cause. Patients who do suffer from vision loss would, however, always be able to see something. Faces may become blurred, print may become illegible, yet they would always be able to get around without the aid of a seeing eye dog.

What percentage experience bleeding? Can trauma and straining cause retinal hemorrhage?

It is well documented in literature that hemorrhaging can occur from trauma, therefore prevention is important. Doctors recommend wearing protective eye wear when engaging in racquet sports and to avoid unnecessary straining, such as at bowel movements, constipation, and weight training. A hemorrhage from straining would only occur if there was an established area of choroidal neovascularization, or fragile vessels. A hemorrhage from straining would be unlikely to occur in the presence of angioid streaks alone.

Can retinal hemorrhage result from cataract surgery?

Luckily, cataract surgery is done in a much safer way than years ago when the surgeon went inside the eye with very small instruments. Yet, while it is safer, there are still some increases and decreases in the pressure of the eye fluid as these instruments enter and exit the eye, making hemorrhaging possible. However, usually hemorrhages from mild kinds of manipulations would only happen if vessels were in a fragile state prior to surgery.

Is there a standardized procedure for determining one's visual acuity?

The only standard procedure available is the use of the Snellen Eye Chart. It measures visual angles using different size letters, and is a fairly standard procedure.

Has double vision ever been reported?

Distorted vision is frequently confused with double vision. This can be caused from a streak coming close to the fovea, center of the macula, or from a laser scar being very close to the center of the macula. The result is a ghost image. A person may be seeing a clear image with one eye and a distorted image with the other, and therefore it is interpreted as a double image. However, if one eye has lost central vision, it is possible that the mechanism that the brain uses to keep the eyes aligned will become less effective because the eyes are not seeing two identical images anymore. The eyes then deviate resulting in some double vision.

Does the location of angioid streaks have any relation to vision loss?

An angioid streak can actually pass through the very center of the retina, through the macula. However there has only been one documented case of this causing legal blindness. It is the proximity of the streak in relation to the center of the eye that increases the risk of vision loss. If one gets a complication of fragile vessels and a subsequent hemorrhage, it is of no concern if it is not in the center of the eye. Unfortunately, if it does occur in the center of the eye one loses detail vision.

Have lasers changed over the last ten years?

Lasers have not changed dramatically over the past ten years. Traditionally twenty years ago there were two types of lasers available; a blue laser and a xenon arc. Today there are different wavelengths available for retinal surgery varying from yellow to red, and even filtering out part of the blue light to use green. An experimental procedure called photodynamic therapy uses a new type of laser and is somewhat of a lighter treatment. The goal of the retina surgeon is to ultimately preserve the very center of the eye. Many times surgeons need to sacrifice an area of retina which is very close to the center of the eye because vessels are present there. Some vision loss can occur during laser surgery if the vessels are so close to the center of the eye that avoiding them with the laser is almost impossible.

What is the present feeling regarding the use of laser in treating retinal hemorrhages?

Patients are generally categorized into three groups. The first group is those patients who have blood vessels which are not near the center. These vessels are known as eccentric and quite easy to treat. The second group contains patients who have vessels which are juxtafoveal, adjacent to the center. Data suggests that juxtafoveal lesions are safe to treat and there is a definite treatment benefit, however some vision loss could possibly occur. Thus it is the comparison between a scar from laser with the scar from observation. Basically, if the surgeon feels that he could treat the threatening lesion without interfering with the center of the eye, it is strongly recommended. If there is going to be some decreased vision from the laser treatment this becomes something which must be discussed with the patient. Patients need to be ready to sacrifice six lines on the eye chart to be better off in the following two years, and this can be a very hard decision to make. Unfortunately the percentage of patients which fit into the first two categories only amounts to about 7%, thus leaving 93% of patients in the third category. These patients have vessels under the center of the eye. Typically if these patients undergo laser surgery they will have worse vision. There is a long term treatment benefit with an immediate sacrifice, however, the benefit is very small. Therefore it is not adopted as a widespread treatment. There is, however, statistical data to support treating small lesions and small vessels that are in the center of the eye, if vision is already reduced to the level of 20/200 or worse. This is the only category of patients which have a benefit.

Obviously, a better treatment is needed than laser photocoagulation for 93% of patients. There are a couple key points to touch upon. First we keep hearing about lasering hemorrhages: we do laser hemorrhages, we laser the fragile vessels to decrease the risk of a hemorrhage. Unfortunately, if the hemorrhage spreads to the center of the eye it will leave some damage when it eventually absorbs, such as a scar or decreased vision. Secondly, fluorescein angiograms should not be recommended as part of a screening examination because there is a 1 in 10,000 risk of allergic reaction. This procedure is also mildly invasive and can be uncomfortable, with many photographs being taken at once. A streak that is close to the fovea will most likely be noticed on a routine ophthalmoscopy. And lastly, a point about the use of ICG screening in children.

ICG is the injection of a dye into the eye. Although it is a relatively safe dye, there are allergies in people who are allergic to iodine. While this test may locate patients at risk for eye problems at an earlier age because of its sensitivity to peau d'orange, it is not recommended as a screening tool.

Treatment Options

Discussed below are treatments such as:

Prednisone, steroids in general, photodynamic therapy, radiation, retinal transplants, surgical removal of blood vessels, and sub-retinal surgery. Any of these treatment options would have to be considered unproven. The only proven strategy to date is laser treatment involving blood vessels which are not directly in the center of the eye.

Steroids Many doctors and patients will agree that steroids are beneficial, however there is no scientific data available at this time. Steroids are very helpful in inflammatory conditions, and while abnormal vessels are not related to inflammation, steroids may help in stabilization of vision. Steroids have many side effects, and need to be used with caution. They have systemic side effects such as elevated blood pressure, as well as ocular side effects, such as cataracts and glaucoma and therefore need to be used under the direction of a physician.

Photodynamic Therapy Photodynamic therapy is a procedure in which a porphyrin type material is injected into abnormal blood vessels that are proliferating. With this chemical injected into the vessels, a light of lower intensity is used. The problem with this, while it is safe and does not damage the normal retinal tissue, is that these abnormal vessels tend to reopen after a few weeks to months. It may, in the future, have a very important role. Much research is done with abnormal blood vessels (pathologic angiogenesis), and as inhibitors of angiogenesis come on the market and are tested we have peptides and antibodies against these angiogenic substances. By combining therapies you could treat someone with photodynamic therapy and close their vessels for several weeks to months until we could give them a pharmacological agent that works. Ultimately there will be a role for pharmacology and photodynamic therapy in the future.

Radiation Low dose radiation is still being studied. However preliminary results suggest that the patients who are in the placebo group, those who receive no treatment, do slightly better than patients who have received low dose radiation. It is important to remember that science takes a long time to perfect new treatments and consider their value to the patients.

Retinal Transplants Retinal transplantation is a procedure which is still in its early stages of development. Unfortunately it does not relate to patients with PXE, who at worst lose their central vision and do not suffer from complete blindness.

Surgical Removal of Blood Vessels The surgical removal of blood vessels is a procedure which was pioneered by a group at Washington University in St. Louis. This type of procedure is to curb macular degeneration. In recent years, most of the pioneers have abandoned it due to many complications and low improvement rate. Complications occur during the removal of blood vessels. To remove blood vessels the

surgeon must go inside the eye and remove the vitreous jelly. Then a small hole is made in the retina. The surgeon proceeds underneath the retina to remove the abnormal blood vessels. Unfortunately during this process some of the pigment epithelium is removed with the vessels, which is necessary for good vision. Thus even if abnormal blood vessels are removed, vision does not seem to be positively influenced. There is a role for the surgical removal of blood vessels where there is limited disease, such as in a case of trauma or nearsighted person who has a tiny crack through which blood vessels grew. In such cases removal is easier and more rewarding to the patient.