GRAND ROUNDS™

GRAND ROUNDS SAMPLE OPINION

Condition 1: Breast cancer

Names and details have been changed to protect patient privacy.

EXPERT OPINION PROVIDED BY:

Dr. Lidia Schapira

Medical Oncologist
Breast Oncology, Dana Farber Harvard Cancer Center

Associate Professor
Department of Medicine, Harvard Medical School

Associate Professor
Medicine, Massachusetts General Hospital

ABOUT DR. SHAPIRA

Dr. Lidia Schapira is an Assistant Professor of Medicine at Harvard University and a medical oncologist at the Gillette Center for Breast Oncology at Massachusetts General Hospital. Her clinical area of expertise includes breast cancer, new treatments for the disease, and the special concerns for young cancer survivors. Her research focuses on the psychosocial support of cancer patients and improved communication between the patient and treating physician. Dr. Schapira is the editor of the Art of Oncology (AOO) collection in the Journal of Clinical Oncology (JCO). Dr. Schapira has published articles in the leading scientific and academic journals in the field and is a past director of the American Psychosocial Oncology Society.

EDUCATION

Medical School Dartmouth Medical School

Residency Beth Israel Deaconess Medical Center

Fellowship Brigham and Women's Hospital

AWARDS

Board of Directors, American Psychosocial Oncology Society

Statesman Award, American Society of Clinical Oncology

Fellow, American Society of Clinical Oncology (ASCO)

SELECTED PUBLICATIONS

Rosenberg SM, Tamimi RM, Gelber S, Ruddy KJ, Bober SL, Kereakoglow S, Borges VF, Come SE, **Schapira L**, Partridge AH. Treatment-related amenorrhea and sexual functioning in young breast cancer survivors. Cancer. 2014 May 28.

Partridge AH, Ruddy KJ, Gelber S, **Schapira L**, Abusief M, Meyer M, Ginsburg E. Ovarian reserve in women who remain premenopausal after chemotherapy for early stage breast cancer. Fertil Steril. 2009 Apr 29.

Eichler AF, Kuter I, Ryan P, **Schapira L**, Younger J, Henson JW. Survival in patients with brain metastases from breast cancer: the importance of HER-2 status. Cancer. 2008 Jun;112(11):2359-67.

SUMMARY FOR THE PATIENT

Thank you for allowing me to review your case and provide my opinion. Before I answer your questions and provide my recommendations, let me summarize your medical history and concerns based on what I have learned from your medical records and the questionnaire you completed.

You are 36 years old and were initially evaluated by your gynecologist in February of this year because you felt a lump in your breast. Your doctor also felt a firm mass above your areola and referred you for a diagnostic mammogram. The mammogram did not detect any specific abnormality but an ultrasound of your breast, which was performed the same day, demonstrated a solid mass.

A biopsy of the mass was performed on March 26th. Pathology revealed infiltrating ductal carcinoma (infiltrating ductal carcinoma arises in the ducts of the breast and spreads to the surrounding breast tissue; it is the most common type of breast cancer.) You subsequently underwent an MRI scan of the left breast which demonstrated the mass. There was, however, no evidence that your lymph nodes were enlarged (enlarged nodes would have suggested that the tumor had spread).

On April 2nd, your case was discussed by a group of doctors including a surgical oncologist, a medical oncologist, and a radiation oncologist. Given the location and size of the tumor and your desire for breast preservation, your doctors recommended that your treatment start with chemotherapy followed by either a lumpectomy or mastectomy (depending on how your tumor responds to the chemotherapy). You were also seen by a genetic counselor and testing for genetic mutations related to breast cancer were performed (the results are not yet available). You have no known family history of breast or ovarian cancer.

On April 9th, you underwent a sentinel lymph node biopsy (removal of nearby lymph nodes to determine if your cancer had spread) and a port was placed in preparation for chemotherapy. The sentinel node did not show signs of cancer. The following day, you had a CT scan of your abdomen, chest and pelvis performed; the scan was negative, suggesting that your disease had not metastasized or spread.

You saw your oncologist on April 15th who recommended immediate chemotherapy with Adriamycin and Cytoxan, followed by surgery and post-operative paclitaxel (another type of chemotherapy). You received your first course of Adriamycin and Cytoxan later that day.

You are interested in identifying the best course of therapy for treating your breast cancer. You recognize that you have two surgical options—total mastectomy and lumpectomy—and want to better understand the advantages and disadvantages of these approaches. Because of your young age, you are also understandably concerned about how treatment may impact your ability to conceive later on.

PATIENT'S QUESTIONS

I'd like to start by pointing out that, while a cancer diagnosis is extremely frightening, you have several important things working in your favor. Perhaps the most important is the fact that your imaging studies and biopsy results suggest that your cancer has not spread beyond your breast. Also, your care so far has been excellent, and your medical team has been very thoughtful about the next steps in your treatment plan. So, now, let's talk about your specific questions regarding your treatment.

What is the best course of therapy to treat my breast cancer? Is a lumpectomy as effective as a mastectomy if I undergo chemotherapy first and have a good response to it?

The best course of therapy to treat your cancer is a combination of chemotherapy, hormonal (endocrine) therapy, surgery and possibly, radiation therapy.

A lumpectomy plus radiation is as effective as a mastectomy. Although there might be a tiny benefit to having a mastectomy, it is not sufficient for me to recommend this approach over breast conservation. Some young patients prefer to have mastectomies because they feel that they will not be as anxious about the follow-up, but let me reassure you that if your team feels that you can conserve your breast, you will be fine doing so. It is important to make sure that the surgery removes not only the tumor remaining after chemotherapy but also a small amount of normal tissue around it; this is called a 'margin'. Especially for younger women, this is an important aspect of a good treatment plan.

If your genetic tests come back and you are found to have a BRCA mutation, then my advice would be different. I would encourage you to at least consider having bilateral mastectomies and, should you desire it, to have breast reconstruction. Some carriers of BRCA mutations opt to keep their breast but they must have frequent follow up exams, typically every six months, and also have regular screening MRIs while they are young.

If you undergo a lumpectomy, you will need radiation therapy afterwards. You may or may not need radiation therapy if you have a mastectomy; the need for radiation will depend on the tumor's size, the presence or absence of lymph node involvement, and the tumor's pathology (i.e. if it has concerning features when it is examined under the microscope after your surgery). With a tumor that is <5cm and node negative (i.e. the tumor has not spread to the lymph nodes), it is possible that you may not need radiation. However, if the tumor's pathology is at all worrisome, your doctors may recommend radiation even if you have the entire breast removed.

The choice to have chemotherapy before surgery is a reasonable one if the intention is to shrink the tumor enough to allow for breast conservation. I understand that you are receiving chemotherapy with Adriamycin and Cytoxan every two weeks and get Neulasta shots to boost the recovery of your bone marrow. Your oncologist also recommended weekly Taxol after your surgery for 12 weeks. This is ok - but not the only approach. We often deliver all of the chemotherapy pre-operatively. Some

women's tumors respond better to Taxol than to Adriamycin and Cytoxan - so it makes sense to give all the chemotherapy before the surgery, rather than splitting it into two. I am not sure why your team recommended the 'split' approach; you may want to ask. In terms of efficacy, it probably will result in the same benefit.

Following this treatment, you will be prescribed tamoxifen for at least five years. Tamoxifen is a drug that interferes with estrogen's ability to stimulate the growth of breast cancer cells. Studies are underway to see if adding a short period of ovarian suppression (ovarian suppression involves the use of medical therapies to temporarily shut down the function of the ovaries) in addition to tamoxifen may also help improve outcomes but, at the moment, it is not considered standard care. The American Society of Clinical Oncology does not recommend adding ovarian suppressive therapy for women in your age group.

How will chemotherapy impact my ability to get pregnant? Is there anything that I should do or any precautions that I should take to protect my fertility?

Your concerns about protecting your fertility during treatment are completely understandable. Chemotherapy will, in fact, affect your ovaries and may interfere with your ability to have a biological child in the future. That said, almost all women your age that receive this type of chemotherapy (Adriamycin, Cytoxan and Taxol) recover their periods and are then able to conceive several years later. The younger you are when you receive chemotherapy, the more likely you are to preserve your fertility.

At this time, there is nothing else you can do to protect your fertility. Some gynecologists have recommended the use of leuprolide injections (leuprolide stops the release of estrogen from the ovaries) during chemotherapy to help preserve fertility. There have been several clinical trials that have studied this approach, but there have been no conclusive results. For this reason, leuprolide is not used commonly because the benefits remain unproven.

Thinking about your fertility, it is also important to consider the impact of tamoxifen on the timing of a pregnancy. Because you cannot get pregnant while on tamoxifen (it could cause harm to the developing fetus), its use will delay the time that you can think of having a biological child. Some women opt to take this treatment for a shorter period, but they may be risking a cancer recurrence. These are tough choices to make and you will need to think through this issue in a few years with your partner as well as your medical team. So, in the end, it is not just the chemotherapy that may affect your fertility, but also having to wait until you can safely get pregnant.

As you know, age alone can have an impact on fertility (i.e. the older you are, the more difficult it may be to conceive). It is good that you are thinking about fertility now, but please know that many women have been able to conceive after beating breast cancer.

I noted in your chart that you marked your level of distress as 8/10 and that you feel sad, tearful and depressed. This may very well be a normal reaction given the diagnosis you just received. I have listed two sites you may find helpful - both organizations provide information to young women and also support groups, chatrooms and advice. I hope things go smoothly for you and that you find enough support among friends, medical caregivers and family.

RECOMMENDATIONS FOR THE PATIENT

The results of BRCA testing will inform your surgical options.

- If you do not have a BRCA mutation, then a mastectomy is not necessary unless there is no shrinkage of your tumor with chemotherapy and your surgeon does not feel that he or she can perform a lumpectomy.
- If you have a BRCA mutation, I would encourage you to at least consider having bilateral mastectomies with breast reconstruction.

Continue with the chemotherapy medications that have been recommended. Your team of doctors, however, may want to consider giving you all the chemotherapy upfront (i.e., before surgery), especially if your response to Adriamycin and Cytoxan chemotherapy is not great and further shrinkage is needed in order to conserve the breast.

If you undergo a lumpectomy, you will need radiation therapy afterwards. You may or may not need radiation therapy if you have a mastectomy.

Following local treatment (i.e. surgery, radiation therapy), you will be prescribed tamoxifen for at least five years.

REFERENCES FOR THE PATIENT

http://www.cancer.net/sites/cancer.net/files/asco_answers_guide_breast.pdf

REFERENCES FOR THE TREATING PHYSICIAN

Prospective study of fertility concerns and preservation strategies in young women with breast cancer.

Ruddy KJ, Gelber SI, Tamimi RM, Ginsburg ES, Schapira L, Come SE, Borges VF, Meyer ME, Partridge AH.
J Clin Oncol. 2014 Apr 10;32(11):1151-6

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Condition 2: Colon cancer

Names and details have been changed to protect patient privacy.

EXPERT OPINION PROVIDED BY:

Andrew Chan

Program Director,
Gastroenterology Training Program
Massachusetts General Hospital

ABOUT DR. CHAN

Dr. Andrew Chan, MD, MPH, is the Program Director for the Gastroenterology Training Program at Massachusetts General Hospital (MGH). Dr. Chan received both his medical degree and masters of public health degree at Harvard University and went on to complete both his residency and fellowship programs at MGH. He is Board Certified in Gastroenterology and has clinical interests in general gastroenterology, gastrointestinal cancer, cancer prevention, colon and rectal cancer, and cancer risk assessment.

EDUCATION

Medical School Harvard Medical School

Residency Massachusetts General Hospital

Fellowship Massachusetts General Hospital

AWARDS

American Society of Clinical Oncology heralded Dr. Chan's research as one of the 18 most notable advances in cancer research (2007)

SELECTED PUBLICATIONS

Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013. 369(12):1095-105.

Aspirin use and risk of colorectal cancer according to BRAF mutation status. JAMA. 2013. 309: 2563-71.

Inflammatory markers are associated with risk of colorectal cancer and chemopreventative response to anti-inflammatory drugs. Gastroenterology. 2011. 140(3): 799-808.

Aspirin use and survival after diagnosis of colorectal cancer. JAMA. 2009;302(6):649-58.

SUMMARY FOR THE PATIENT

Thank you for allowing me to review your case and provide my opinion. Before I answer your questions and offer my recommendations, let me summarize your medical history and concerns based on what I have learned from your medical records and the questionnaire you completed.

You are 40 years old and were diagnosed with stage I colon cancer in 2012. In November 2012, you underwent a colonoscopy because you had noted blood in your stools on two occasions. A large polyp was removed during the procedure that was concerning, so you underwent a right hemicolectomy (removal of the right side of the colon) that December. While cancerous changes were found in the polyp, your doctors felt that it had been entirely removed. There was no evidence that the cancer had spread to nearby lymph nodes or elsewhere in your body.

You have undergone genetic testing and counseling to determine if you are at increased risk for developing colon cancer again in the future. So far, the evaluation does not suggest that you are. You have been getting regular CT scans and visiting with your oncologist every six months to monitor your situation. You have also been undergoing annual colonoscopy; although you had polyps removed both in December 2013 and December 2014, there was no evidence of cancer. You doctor has also been monitoring your carcinoembryonic antigen level (or CEA; elevated levels of CEA can be a sign of cancer), which has remained in the normal range.

I understand you are also currently being evaluated for several nodules in your thyroid as well as a nodule in your adrenal gland.

You would like to identify the best screening protocol for colon cancer given your history and to better understand your future risk of developing colon cancer. You are also concerned that different radiologists have read each of your imaging studies and that the readings are not comparable.

PATIENT'S QUESTIONS

I'd like to start by acknowledging how frightening a cancer diagnosis can be and say that your concerns about your cancer care are completely understandable. You have several important things working in your favor however. Perhaps the most important is the fact that your cancer was diagnosed at a very early stage and that your physicians believe it was successfully removed. Also, your care so far has been excellent, and your medical team has been very thoughtful about your follow-up.

I'd also like to briefly discuss stage I colon cancer. Although you are probably already very familiar with the topic, I think the information will provide a useful framework for my recommendations. Staging is a way of describing how far cancer has progressed; colon cancer stages range from Stage 0 (the least advanced) to Stage IV (the most advanced). In general, the earlier stages of cancer are associated with better outcomes. In Stage 0 (or carcinoma in situ) colon cancer, abnormal cells are confined to the innermost layer of the intestinal wall; in Stage IV cancer, cancer has spread beyond the colon to distant organs such as the liver or brain. In Stage I cancer (which you were diagnosed with), the cancer has penetrated through the innermost layer of the intestinal wall into the layer of tissue just beneath it (called the submucosa). The treatment of most Stage I colon cancers is a colectomy (surgical removal of the involved portion of the colon) which, in most cases, is curative.

I'd like to now address your specific questions.

I was diagnosed with WPW, wanted to get a second opinion on whether it's the right diagnosis.

The goal of the colon cancer screening that you have been undergoing (i.e. repeat CT scans, visits with your oncologist, CEA measurements, and colonoscopies) is to identify a cancer recurrence or the development of a new tumor as early as possible. I do believe that seeing your doctor annually to monitor your colon cancer is adequate. In fact, by clinical guidelines, we currently do not recommend regular monitoring for individuals who have had a stage T1N0 colon cancer. ("T" refers to the tumor's size and "N" designates involvement of nearby lymph nodes; T1N0 represents an early stage tumor that has not spread to nearby lymph nodes.) Thus, the fact that you are seeing a doctor to monitor for colon cancer once a year is more than what is typically done.

That said, I think it is reasonable for you to continue your annual check-ups with your colon cancer doctors. Also, because polyps have been identified on each of your recent colonoscopies, I think it makes sense to continue to have them each year. I do not, however, think that you need to continue having your CEA levels checked.

Can you please explain a bit about the genetic testing that has been done and what it suggests about my risk of developing polyps and/or colon cancer in the future? Am I at increased risk?

You had genetic testing for the two most common polyposis syndromes (conditions associated with the development of numerous polyps in the colon) -- familial adenomatous polyposis syndrome and MYH-polyposis. I suspect that your doctors ordered these tests because you have exhibited some predisposition to developing polyps. I am not, however, surprised that you tested negative for these syndromes since you have not actually had many polyps. Most patients with familial polyposis or MYH-polyposis tend to get at least a dozen polyps over their lifetime. You have not had such a large number of polyps.

I did not see it mentioned in your medical records, but I wonder if you also have been tested for Lynch syndrome. Lynch syndrome is the most common hereditary (inherited) colon cancer syndrome. It is characterized by early onset colon cancer usually without a significant number of polyps. Individuals with Lynch syndrome have a higher risk of developing a number of other types of cancer as well, including cancer of the stomach and liver, and women with Lynch syndrome are at increased risk of ovarian and uterine cancer. In many ways, your clinical presentation would be more characteristic of Lynch syndrome, and I would recommend that you consider being evaluated for it. In most cases, a simple blood test can be used to determine if someone has Lynch syndrome; the test identifies gene mutations (abnormalities) associated with the condition.

My imaging studies are being read by a different doctor each time they are performed. How do I know if my scans are being compared appropriately? Do you think it would be helpful to have one radiologist review all of my images together?

Typically, the reports associated with your radiology imaging will note if they have been compared with prior studies (and note the specific study that was compared). For the most part, standard radiology studies do not need to be reviewed by a single radiologist. (One might even argue that it's nice to have different doctors review the studies because you get more fresh eyes on them). The findings you have had are common enough that I think having different readers will not appreciably affect things for you. On the other hand, if you were able to have a single radiologist review all of your images, that would be the ideal.

RECOMMENDATIONS FOR THE PATIENT

Thank you, XXXXX, for allowing me to participate in your care. In summary:

- *Continue your annual check-ups with your colon cancer doctors. A yearly colonoscopy is also probably reasonable since you have had polyps on each of your exams. I do not think regular CEA testing is warranted.*
- *Talk to your doctor about undergoing testing for Lynch syndrome.*
- *Now that you have had abnormalities noted in your thyroid gland, adrenal gland, and lung, it is important that you have those followed up by your primary doctors. I do not think these findings are at all related to your colon cancer. It is more likely that these are unrelated findings altogether.*

I hope that you find my recommendations helpful and that they serve as the basis for a productive conversation with your treating team. I wish you good fortune with your health.

REFERENCES FOR THE PATIENT

Follow-up screening for colon cancer

http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-treating-by-stage-...

http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-after-follow-up

http://www.nccn.org/patients/guidelines/colon/index.html#38

Lynch Syndrome

http://ghr.nlm.nih.gov/condition/lynch-syndrome

http://www.cdc.gov/features/lynchsyndrome/

REFERENCES FOR THE TREATING PHYSICIAN

Current NCCN guidelines regarding follow-up for patients with a history of colon cancer

http://www.tri-kobe.org/nccn/guideline/colorectal/english/colon.pdf

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Condition 3: Musculoskeletal

Names and details have been changed to protect patient privacy.

EXPERT OPINION PROVIDED BY:

Dr. Greg Gebauer

Orthopedic Surgeon
Advanced Orthopedic Center

ABOUT DR. GEBAUER

Dr. Gregory Gebauer specializes in operative and non-operative treatment of spinal disorders and has special interests in minimally invasive procedures, cervical myelopathy, degenerative scoliosis, lumbar stenosis and the aging spine. While training in Baltimore, Dr. Gebauer served on the orthopedic team caring for the Baltimore Orioles and completed a trauma rotation at the Adam Crowley Shock-Trauma Center. In addition to his clinical work, Dr Gebauer has authored multiple book chapters and research papers on topics such as osteoporotic compression fractures, minimally invasive spine surgery, spinal tumors and spine trauma.

EDUCATION

Masters of Science Rutgers University

Medical School University of Medicine and Dentistry of New Jersey

Residency Johns Hopkins University Hospital

Fellowship – Orthopedic and Neurosurgical Spine Fellowship Rothman Institute at Thomas Jefferson University Hospital

AWARDS

Alpha-Omega-Alpha Honors

Member, American Academy of Orthopaedic Surgeons

Member, North American Spine Society

SELECTED PUBLICATIONS

Spinal cord injury resulting from injury missed on CT scan: the danger of relying on CT alone for collar removal. **Gebauer GP**, Osterman M, Harrop J, Vaccaro A. Clin Orthop Relat Res. 2012 Jun;470(6):1652-7.

Magnetic resonance imaging of spine tumors: classification, differential diagnosis, and spectrum of disease. **Gebauer GP**, Farjoodi P, Sciubba DM, Gokaslan ZL, Riley LH 3rd, Wasserman BA, Khanna AJ. J Bone Joint Surg Am. 2008 Nov; 90 Suppl 4:146-62.

Low-intensity pulsed ultrasound increases the fracture callus strength in diabetic BB Wistar rats but does not affect cellular proliferation. **Gebauer GP**, Lin SS, Beam HA, Vieira P, Parsons JR. J Orthop Res. 2002 May;20(3):587-92.

SUMMARY FOR THE PATIENT

Thank you for allowing me to review your case and provide my opinion. Before I answer your questions and offer my recommendations, let me summarize your medical history and concerns based on what I have learned from your medical records and the questionnaire you completed.

You are XX years old and developed pain in your back and right leg in August of XXXX. You consulted with several orthopedic surgeons, and had an MRI of your spine that showed you had a herniated disc and degenerative changes. You ended up having surgery to remove a portion of the damaged disc (a procedure called a microdiscectomy) last September. Unfortunately, since your surgery, you have had difficulty lifting the front of your right foot (called "foot drop") as well as some numbness and pain in the foot. You have undergone physical therapy and have tried the medication Neurontin (gabapentin) for your symptoms; you also received two epidural steroid injections (spinal injections.) Although your leg pain improved with the injections, unfortunately, your foot drop and numbness have persisted and your doctors have recommended that you have additional surgery.

You would like to understand the cause of your symptoms and confirm the diagnosis you have been given. You are confused about whether or not you should proceed with the surgery that has been recommended or if there are alternative treatments that you should consider. Finally, you would also like to understand if your foot drop is permanent or if it will improve with surgery.

PATIENT'S QUESTIONS

First of all, let me say that I think your treatment to date has been appropriate and very much in keeping with what I would have recommended. Before I answer your specific questions, I'd like to first provide you with a bit of background about the spine and intervertebral discs. Although you may already be familiar with much of this information, I think that reviewing this information will help clarify the recommendations that I'm going to make.

The spinal cord is a long bundle of nerve tissue that extends from the brain and down the back; the cord is protected by the spine, which is made up of bones called vertebrae. The vertebrae are divided into segments that control different parts of the body. There are four major segments of the spinal cord: the cervical (C), thoracic (T), lumbar (L), and sacral spine (S). At every level of the spinal cord, pairs of spinal nerves branch off and travel to other parts of the body where they control both movement and senses (for example, pain, temperature, touch, etc.). The vertebrae and spinal nerves are numbered (e.g. L4, L5, etc.).

Between each of the vertebrae of the spine sit intervertebral discs, often referred to simply as 'discs'. Discs act as shock absorbers and facilitate motion in the spine. They are composed of a central watery gel (called the nucleus), which is surrounded by tough fibers (called the annulus). As discs wear out, the gel inside begins to lose water and dry out; this causes discs to collapse and can potentially cause parts of the disc to bulge or herniate into the spinal canal. Over time, everyone experiences some amount of disc degeneration.

When discs begin to bulge or herniate, they may place pressure on nearby spinal nerves causing what is called 'radiculopathy'. Radiculopathy involving the lumbar spine can trigger sharp pain that extends from the low back into one or both legs; it can also cause numbness or weakness in the legs and feet.

What is causing my symptoms? Is surgery the best treatment for this? Are there other treatments I should consider?

The pain you were having prior to surgery was consistent with the disc herniation and stenosis at the L4-5 spinal level that was seen on your MRI. One of the doctors you consulted with recommended a procedure called a L2-L5 laminectomy (surgical removal of parts of your vertebrae). In my opinion, this would have been more surgery than what you needed to help you with your problem, and I would not have suggested it. You then sought care of a different surgeon, and the surgery that was performed (an L4-L5 microdiscetomy), was appropriate for the problems you were having and the findings seen on your MRI.

My understanding is that your main concern at this point is weakness in your right leg (the foot drop) that began following your surgery. There are two possible causes for this. The first is that your surgery may not have entirely fixed the underlying problem: pressure on your spinal nerve. There could be residual pressure on the nerve that is causing the nerve to function improperly. In fact, the first MRI that you had after surgery in October showed that there was still some pressure on the nerve, though most of this pressure appeared to be due to normal swelling and granulation tissue (tissue your body makes as it's healing) that we would expect to see after a surgery. Although your more recent MRI from January showed that a significant portion of the swelling and granulation tissue had resolved (and the pressure on the nerve had lessened), some pressure on the nerve persists. The pressure appears to be mostly from arthritic changes in the bones of your low back rather than from scar tissue from your surgery (although there is still a small amount of scar tissue that can still be seen). In my opinion, the amount of pressure on the nerve is relatively mild, but it is still there.

The other possible cause of your foot drop is nerve damage from surgery. Manipulation of the nerve during surgery could have damaged it, or, alternatively, the nerve could have been injured by swelling and scarring that development post-operatively. This is a rare but known complication of this type of surgery. Unfortunately, having diabetes increases the risk of this type of injury. This type of injury to the nerve is called a neuropraxia. Basically, it's similar to a bruise, and while it's typically something that improves over time, it can take a long while. Generally we say that nerves heal about 1mm a day. So if you imagine the length the nerve travels from your low back to your leg, you then can visualize how this can take quite a while to heal (often up to a year).

What you should do at this point is a hard question with no clear answer. If your symptoms are being caused by residual compression on the nerve, then surgery—a procedure called a full laminectomy—could help. A laminectomy would involve removing all of the bone off the back of the spinal canal and fully exploring the nerve to make sure that there is no pressure on it.

Unfortunately, if the weakness in your foot is the result of a nerve injury, then a second surgery won't help and could even make things worse. After looking at your MRI scans, I think that surgery is a possible option, but it is not something that I would recommend. I do not see that there is sufficient pressure on your nerve that I think doing a second surgery would be likely to help you. All procedures carry some risk; in your situation, I believe that an additional surgery has a greater risk of causing additional damage than its potential to help your weakness. If you were to say that you wanted to try everything possible to get your strength back, you could pursue surgery, but, I would recommend against it.

Could my foot drop be permanent? What is the likelihood that it will improve with the treatment you suggest?

At this point, it is too soon to say if your foot drop is going to be permanent or not. As I've already mentioned, nerves take a notoriously long time to heal, often up to a year. I know that it has been 5 months since your surgery, but I would give it more time. In the meantime, I would continue to exercise your leg and back. I know that you have already done physical therapy. But physical therapists will usually give you a home exercise program to do on your own—and this

is something that I would recommend pursuing. Exercising offers a number of benefits. First, it will strengthen the muscles in your leg and help compensate for your weakness. Second, it can stimulate the damaged nerve and aid in its healing. I know it's not a quick fix, but I think that, given time to heal, your leg will improve and that a regular exercise program will help.

Unfortunately, other than adaptive measures (i.e. braces) to help you cope with the weakness, there aren't any other great treatment options that I can suggest. Injections and medications may help with your pain, but they will not improve the weakness. If your foot actually catches or drags as you walk, a brace may help. Sometimes boots or high-top sneakers can also give you some extra support.

I wish there was a fast or easy solution to your problem. I would give your nerves time to heal and continue with an exercise program. Over time, I do believe that you will get better, but, unfortunately, it may take a while.

RECOMMENDATIONS FOR THE PATIENT

Thank you, PATIENT NAME, for allowing me to participate in your care. In summary:

Because your nerve does not seem to be pinched significantly on your most recent MRI, I do not believe that an additional surgery would be beneficial. Instead of surgery, I would recommend continuing with a regular exercise program to strengthen both your back and leg. Although there is a chance that the weakness in your foot could be permanent, over time, I believe that it will improve. It often takes a year or more for this type of injury to resolve. Braces or different shoes may help if your foot drags or catches as your walk.

I hope that you find these recommendations helpful and that they serve as the basis for a productive conversation with your treating team. I wish you good fortune with your health.

REFERENCES FOR THE PATIENT

Information on the anatomy of the spine:
http://orthoinfo.aaos.org/topic.cfm?topic=A00575

Information about foot drop:
http://www.ninds.nih.gov/disorders/foot_drop/foot_drop.htm

grandrounds.com

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Condition 4: Chronic pain

Names and details have been changed to protect patient privacy.

SUMMARY FOR THE PATIENT

Thank you for allowing me to review your case and provide my opinion. Before I go into answering your questions and providing my recommendations, let me summarize your medical history and concerns based on what I've learned from your medical records and the questionnaire you completed. You are a 14 year-old girl who originally presented with right thumb swelling in October of 2011, and subsequently progressed to your right index finger, left hand and wrist. Two years later, your symptoms consisted of significant swelling of your right arm and leg with extreme sensitivity and tenderness, inability to move both your right arm and leg, tenderness to palpation or light touch, and inability to flex and extend your limbs without assistance. These symptoms make you unable to bear weight and leave you wheelchair bound.

Meanwhile, you also have flakiness of your scalp as well as flaking of your right leg after swelling. You had been placed on multiple doses of solumedrol (a steroid), methotrexate, Humira and a prednisone taper for suspected worsening psoriatic arthritis (pain in the joints associated with the skin rash, psoriasis). Your symptoms are only mildly improved with physical therapy but you have recurrent swelling and pain. You have a family history of autoimmune disorders. A serious of blood work for autoimmune diseases, Lyme disease did not reveal a specific diagnosis. Imaging studies including brain, spine and joints were negative. Your physician believes that Reflex Sympathetic Dystrophy (new name is Complex Regional Pain Syndrome) may explain your symptoms, that's why you were on Elavil amitriptyline, and Neurontin.

PATIENT'S QUESTIONS

What is complex regional pain syndrome?

Complex regional pain syndrome (CRPS, as known as reflex sympathetic dystrophy) is a condition that isn't well understood and is often difficult to diagnose. CRPS is an uncommon form of chronic pain that usually affects your limbs. It is a rare, chronic systemic disease and progressive condition characterized by severe pain, inflammation and changes in the skin. The cause of complex regional pain syndrome isn't clearly understood. It typically develops after an injury, infection or surgery. Some of the most common injuries are dog bites, car/motorcycle accidents, slip and fall injuries. The pain is out of proportion to the severity of the initial injury. However, in many cases no previous injury took place. The common symptoms of CRPS include burning sensations and pain, muscle spasms, continuous intense pain throughout the body, swelling and stiffness of joints, motor disability, with decreased ability to move, changes in nail and hair growth patterns and skin changes.

Is this related to my psoriatic arthritis?

We do not know exactly what events trigger CRPS. The cause of complex regional pain syndrome isn't clearly understood. It typically develops after an injury, infection or surgery. Although there's no direct link between psoriatic arthritis and complex regional pain syndrome, one case report describes a case of CRPS type I in a patient with psoriatic arthritis.

What is causing my symptoms - complex regional pain syndrome, psoriatic arthritis, or something else?

It can be difficult to distinguish between complex regional pain syndrome and psoriatic arthritis.

Your symptoms (swelling of your right arm and leg with allodynia - extremely sensitive pain, unable move right arm and leg, tenderness to palpation or light touch, unable to bear weight) could be from complex regional pain syndrome. The symptoms of joint pain, swelling, tenderness and the flakiness of your scalp as well as flaking of your right leg after swelling make this condition similar to classic psoriatic arthritis. It is not impossible is that psoriatic arthritis causes inflammation in and around the joints; this inflammation could be the trigger of CRPS.

We mostly agree that there is probably more than one single cause. That is a combination of different conditions with the same symptoms.

Is the damage to limbs permanent? What is the natural course of this condition - will it spread to my other limbs?

It's difficult to predict how complex regional pain syndrome (CRPS) will progress. In some cases it can last for months or even years, and a few people may be left with some degree of pain permanently. However, in the majority of cases and with good rehabilitation therapy, it can settle over the course of a few weeks or months. Sometimes people who've had CRPS in one limb may develop it in another, but this is fairly unusual.

Do I need additional tests?

Complex regional pain syndrome (CRPS) is often difficult to diagnose since there's no specific test that will confirm the diagnosis. Doctors mainly base diagnosis on symptoms and some other imaging/blood tests to rule out other possible causes of the pain and swelling. Occasionally, a local anesthetic sympathetic block (a numbing technique) is used as a diagnostic test. If this block eases the pain, then it's likely that the sympathetic nervous system is contributing to the pain.

RECOMMENDATIONS

Since I have not had the opportunity to examine you and talk to you face-to-face, I am therefore not your "treating physician". You should use this opinion as a basis of discussion with your treating physician. You need to work with your physician, who can examine you in person, to determine the optimal treatment for you.

As for my recommendations - the key of the treatment is to relieve pain, keep the affected limb mobile, prevent stiffness and loss of muscle tone as well as promoting circulation, and restore as much function as possible to the affected limb and improve quality of life. My recommendation is that a multidisciplinary approach to treatment should be pursued with you through a combination of physical rehabilitation therapies and pain-relieving medication.

Non-medication treatment

Due to the varied symptom presentation, it may be unclear which conservative therapies will be most beneficial in the treatment of CRPS:

1. Rehabilitation therapies may begin very gently to avoid a flare-up of your symptoms, and you'll need to build up the duration and intensity of the therapies gradually, even if progress seems slow at times. Exercise can be difficult if you have severe pain so you'll need to work with your pain doctor to have pain controlled. Your physiotherapist will advise on pain relief therapies such as transcutaneous electrical nerve stimulation (TENS).

2. Desensitisation is a technique your occupational therapist can help with. It is to normalize touch sensations in the affected limb. It involves touching the skin frequently with different-textured fabrics and other substances (for example, wool, silk, cotton wool), gradually working towards the painful areas.

3. Relaxation and/or stress management can help in managing pain on a day-to-day basis. A psychologist will focus on helping with coping techniques which may include stress management and relaxation exercises, acceptance and learning how to ask for the support available.

4. Body perception awareness can be especially helpful for people who develop negative feelings about the affected limb. It encourages people to look at, touch and think about the affected limb as often as possible so that the limb begins to feel a normal part of your body again.

5. A few hospitals offer a new treatment known as mirror visual feedback therapy. Exercises are performed with the aid of a mirror positioned so that the patient sees a reflection of the unaffected limb while the affected limb is hidden from view. Graded motor imagery is another type of rehabilitation which uses mirror

therapy, but it also includes other techniques to try to retrain the brain and improve symptoms. Although these techniques haven't yet been widely used, early research suggests that these therapies may be helpful for some people with CRPS.

6. Trials of new medication have included studies looking at strong anesthetic agents such as ketamine to block inflammation such as anti-TNF and intravenous immunoglobulins (IVIG). These approaches remain very experimental and have so far only been used on very small numbers of patients, with variable results.

Medication treatment

There's no single drug treatment that works for everyone with CRPS, but medications can be useful:

1. Neuromodulatory drugs such as gabapentin can help by reducing pain signals from the nerves to the brain.

2. Non-steroidal anti-inflammatory drugs (NSAIDs) can be helpful, but won't always provide adequate pain relief.

3. Opioid medications (for example, morphine, oxycodone) may be prescribed for very severe pain. It should not be used long-term because of their potential side effects. For example: addiction, respiratory depression, drowsiness and constipation.

4. Antidepressants such as amitriptyline and duloxetine, given in low doses, can also reduce pain signals to the brain.

5. Bisphosphonates, which can be given as tablets or injections, seem to help in some cases, although the reasons for this aren't fully understood. The use of high doses of bisphosphonates in the treatment of CRPS is confirmed in different publications.

6. Topical analgesics, means "applied onto the skin". Capsaicin, a cream made from chilli peppers, relieves pain, although it causes a burning sensation for the first few days so it might not be suitable if a large area or a whole limb is affected. Lidocaine patches contain local anesthetic and can be particularly helpful for people with very sensitive and painful skin.

Recommendations and Links

7. Blocks of the sympathetic nervous system can be one of the options either temporary or permanent. If one of these temporary blocks helps, further blocks may be given from time to time. Alternatively, the doctor may recommend a permanent block, which may be performed either surgically or by injection.

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http://www.medicalnewstoday.com/articles/184338.php

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R.S.G.M Perez, W.W.A Zuurmond, P.D Bezemer, D.J Kuik, A.C van Loenen, J.J de Lange, A.J Zuidhof. The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study. Pain, Volume 102, Issue 3, April 2003, Pages 297-307

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GRAND ROUNDS SAMPLE OPINION

Condition 5: Fertility

Names and details have been changed to protect patient privacy.

EXPERT OPINION PROVIDED BY:

Dr. David Adamson

Medical Director
Laboratories at PAMF Fertility
Physicians of Northern California

Associate Clinical Professor, Obstetrics & Gynecology
University of California, San Francisco School of Medicine

ABOUT DR. ADAMSON

Dr. David Adamson, MD is the Director of Fertility Physicians of Northern California, a private medical practice specializing in reproductive medicine, and is an associate clinical professor at UCSF. He has made outstanding contributions on the subject of assisted reproductive technology. Previously serving as past-president to many national organizations, Dr. Adamson remains active in numerous professional societies and continues to raise awareness of infertility and available options. He has published over 100 articles in peer-reviewed journals and serves as a reviewer for journals in his field.

EDUCATION

Medical School University of Toronto

Residency Toronto General Hospital

Fellowship Stanford University

AWARDS

Outstanding Achievement in Medicine - Santa Clara County Medical Association

Research Committee - Society of Reproductive Surgeons

SELECTED PUBLICATIONS

The International Committee for Monitoring Assisted Reproductive Technology and the World Health Organization Revised Glossary on ART Terminology, 2009. Hum Reprod. 2009 Nov;24(11):2683-7.

World collaborative report on in vitro fertilization, 2000. Fertil Steril. 2006 Jun;85(6):1586-622.

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SUMMARY FOR THE PATIENT

The patient is a 40-year-old Caucasian female who would like to be the surrogate for her twin sister's fertilized eggs. She is undergoing fertility workup and was recently alerted to the presence of a fibroid. She is unaware if the fibroid was present during her prior pregnancies.

She underwent an uncomplicated normal spontaneous vaginal delivery two years ago, and a Mirena IUD was placed on a postpartum visit. This was removed and changed to Reclipsen recently. Her last menstrual period is unknown since changing her birth control method.

She has no history of abnormal Pap smears, no STIs, no intermenstrual bleeding, spotting, or discharge, no dysmenorrhea, dyspareunia, or PMS. She is of Ashkenazi Jewish heritage and underwent genetic screening prior to and during her last pregnancy. She is a cystic fibrosis carrier. However, the eggs used for this surrogacy pregnancy would be her sister's.

Additionally, she noted a palpable breast mass in her left breast, but no mass or suspicious cystic lesion was found on a recent breast ultrasound.

PATIENT'S QUESTIONS

I am a potential compassionate surrogate for my twin-sister's fertilized eggs. The doctors at XXXX University have found a small uterine fibroid. I'd like to know:

1) What effect my uterine fibroid might have on my ability to successfully implant and carry my sister's fertilized eggs to term. Can you put the impact of the fibroid in probabilistic terms? Was the fibroid present during my previous three pregnancies?

2) XXXX University has represented that the fibroid might be removed under local anesthesia with only a 70% chance of success. Why is this the case? Would you recommend the local procedure, or that I proceed directly to a procedure under general anesthesia?

3) What difference in success rate, irrespective of the quality of the fertilized eggs, my surrogacy at 40 years of age would be compared to that of a younger surrogate?

Since I have not had the opportunity to examine you and talk to you face-to-face, I am therefore not your "treating physician". You should use this opinion as a basis of discussion with your treating physician. You need to work with your physician, who can examine you in person, to determine the optimal treatment for you.

Thank you for giving me the opportunity to help you make this decision. I think it is wonderful that you are considering doing this for your twin sister.

You are a 40 year old healthy woman with 3 full term normal vaginal deliveries who is considering being a gestational carrier (surrogate) for your twin sister. A < 1 cm fibroid has been diagnosed on sonohysterogram that apparently is distorting the uterine cavity.

You would like to know some medical aspects of being a surrogate at age 40 and whether or not this fibroid needs to be treated and, if so, what type of anesthesia is appropriate. I have answered your questions in 3 sections and written a summary. I have attached 11 documents regarding your questions and other aspects of surrogacy. Good luck with your decisions.

FIBROIDS

Fibroids, also known as myomas, occur in 20% to 80% of women depending on age and race. They are the commonest reason for hysterectomy in the United States. However, in most women fibroids do not cause problems (the commonest symptoms being heavy and/or irregular bleeding or pelvic pain/pressure) and do not need to be treated. The question of what to do with fibroids in women who are attempting pregnancy or who become pregnant when they have fibroids does not have easy answers.

The reason we don't have simple answers regarding the role of fibroids in infertility and in pregnancy is that we don't have high quality information from good studies. This lack of good information occurs because it is extremely difficult to quantify myomas since different women have different numbers of them, different sizes, and different locations at different times in their reproductive lives. Additionally, it is almost impossible to perform well-controlled clinical trials on surgical patients, women attempting pregnancy and women who are pregnant. The major difficulty in performing good clinical studies is that ethics boards will not approve studies that might affect a pregnancy/baby or studies in which patients will be randomized to either no treatment or major surgery.

Furthermore, women attempting to get pregnant or who are pregnant rarely want to participate in a randomized controlled clinical trial. As a result, high quality clinical information is almost entirely absent when it comes to getting pregnant with fibroids, their impact on pregnancy, whether or not they should be treated, and the results of treatment.

Nevertheless, because fibroids are so common there is a general body of knowledge about them that enables us to make reasonable clinical recommendations for most patients. I will share with you the information that is known about fibroids so that you can understand the basis on which I will make my recommendations to you.

I have reviewed the XXX Hospital medical records and the XXXX University sonohysterogram images, and report and facts related to being a surrogate. The electronic sonohysterogram images are, unfortunately, not clear enough for me to make specific comments, although there do not appear to be any large fibroids and the uterine cavity in the static photos appeared reasonably normal. However, the report states there is a "9x8 mm fibroid arising from anterior wall, mid corpus protruding into cavity". Assuming the physician of record attending the sonohysterogram was there, he is an experienced sonographer and almost certainly would have performed the procedure and interpreted the results highly competently.

It is not possible to know if the fibroids were present during your previous pregnancies. This is a very small fibroid that might have been present for a couple of decades or might have begun to grow in the last couple of years. There is no known way to answer the question of when it first appeared other than by sequential imaging of the uterus over years and that is not possible to do after-the-fact.

The feeling of almost all reproductive endocrinologists and reproductive surgeons, of which I am both, is that if a myoma distorts the uterine cavity it should be removed. There may also be clinical situations in which a single large (e.g. >~ 4cm) fibroid near the uterine cavity or if multiple and/or very large myomas are present they should be removed. It would appear the only consideration in your situation is the former. If, indeed, the myoma distorts the uterine cavity, I would recommend removal before attempting to be a surrogate.

The best available evidence is that the fibroid needs to be surgically removed. It cannot be treated medically or with the insertion of beads through the vascular system or with ultrasound or with heat or cold, although all have been tried unsuccessfully and/or are appropriate for other clinical situations but not yours.

The surgical removal of the fibroid can be achieved either hysteroscopically (through the cervix as an outpatient procedure) or with a minilaparotomy (small transverse incision in the lower abdomen) or sometimes at laparoscopy (a small sub-umbilical incision as an outpatient procedure). Since this fibroid is both small and also distorting the uterine cavity it would be preferable to approach it with a hysteroscope through the cervix. However, in order to remove the fibroid with a hysteroscope it is generally felt that 50% or more of the fibroid must be in the uterine cavity, the balance being in the uterine wall, i.e. the largest diameter of the fibroid should be within the uterine cavity, not in the uterine wall. Excellent surgeons can probably remove fibroids when only about 40% are in the cavity. For a fibroid that is this small, if it cannot be removed hysteroscopically one has

Recommendations and Links

to question whether with only 3 or 4 mm in the uterine cavity it is really going to matter at all in a pregnancy. It might be helpful to obtain an MRI of the uterus to understand better exactly the size of the fibroid and how much is in the cavity. I would not state that I would not do a laparoscopy or mini-laparotomy to remove this myoma but I am inclined to think that if it could not be removed hysteroscopically it would be reasonable to leave it alone. But I would want the additional information from an MRI before making that decision.

You have asked for a probabilistic estimate of the impact of the myoma. There are no data on which to make such an estimate. However, based only on clinical and surgical experience, I would estimate the reduction in pregnancy rate without treatment at the 20-40% range. Since the live birth rate per cycle start is approximately 25%, if the fibroid is not treated I would estimate the live birth rate at 15% to 20% on one transfer. If all the embryos are good quality I would transfer 3 embryos on day 3 or 2 blastocysts on day 5, all things considered (there are many other factors in the cycle that could change this number). Generally, but not always, in a woman age 40 (egg source) I would recommend transferring 3 good quality cleaved embryos on day 3 and not growing to blastocyst. There is some chance, maybe about 20-25%, that there may be sufficient embryos to cryopreserve. If so, subsequent transfer of 3 cleaved, good quality cryopreserved-thawed embryos would carry a similar pregnancy rate. If the fibroid is successfully treated, the pregnancy rate would be the 25% because complete resolution ("cure") of its impact would be expected I believe the anesthesia is the least important consideration. A general anesthetic would be common, but it is also possible that a hysteroscopic procedure could be performed under monitored anesthesia care (MAC) with intravenous sedation. I would ask again why that would not be an acceptable anesthetic for this procedure. The surgeon might well want general anesthesia because it is gives a little more control of the patient which can be important when doing hysteroscopic resection and trying to get the very best technical result. All things considered, I would go with the recommendation of the surgeon and do the general anesthesia if that is what is recommended. While certainly complications can occur with any anesthesia, either anesthetic should be extremely safe and not of significant concern for a healthy 40 year old woman with such a minor procedure.

AGE OF SURROGATE

Most women age 40 can carry and deliver a baby without any significant increase in risk to their health. I have attached some slides which, unfortunately, did not reproduce well from the Internet, but can be summarized as follows.

The success rate of the implantation of the embryos will be based almost entirely on the quality and number of the embryos transferred. The slide from SART CDC that is attached shows that the live birth rate per transfer is essentially the same at age 40 as for younger women. Therefore, your ability to get pregnant based on your uterus function should be the same as that of younger women.

However, since your twin sister will be providing the eggs the pregnancy rate (i.e. your pregnancy rate) will be that of a 40 year old woman using her own eggs. The numbers in the graphs are, of course, just averages. Your sister should have the following tests performed to assess ovarian reserve: Follicle Stimulating Hormone (FSH), Estradiol (E2), Anti Mullerian Hormone (AMH), and Antral Follicle Count (AFC). While these tests give some idea of response to ovarian stimulation but have very limited, if any, ability to predict pregnancy rates.

The slides show that maternal mortality is increased approximately 4 times on average for a woman age 40 compared to a woman in her 20s. However, you are in the most favorable category based on race, marital status, and the quality of health care you would receive and this reduces your risk of maternal mortality and morbidity very significantly.

The fact you have had 3 successful natural pregnancies also means that the chances your uterus will work well again is very high. Additionally, I have attached two abstracts that show that your all-cause death rate from being a surrogate would not be statistically different if you did or did not become a surrogate. There may be slightly increased risk as a result of the one elective termination but, with 3 subsequent successful pregnancies, this is likely almost completely irrelevant. While there is always risk with any pregnancy, and the risk would be slightly higher based on age and possibly because this would be your fourth pregnancy, overall you are in the most favorable categories on several factors for good outcome and so there is a high expectation the pregnancy would go well

The interval from your last baby to the next delivery is more than sufficient to optimize outcomes. The IUD and oral contraceptive should have no negative impact.

Therefore, since you are healthy you should be able to conceive at a rate based on the quality and number of embryos produced by your twin sister, you should have a slightly increased but acceptable health risk in pregnancy compared to a younger woman, and your all-cause mortality over the next 3-4 decades should not be significantly different if you did or did not become a surrogate.

ADDITIONAL COMMENTS

The trial catheter check went easily, as expected in a multiparous patient, and suggests that the embryo transfer would be easy to perform and which is a favorable factor for higher pregnancy rates.

I assume your twin sister has been screened as appropriate to be the egg source for a pregnancy, and her husband as well. The screening could be somewhat limited if she is an identical twin, of course.

I have reviewed all of the received XXX Hospital and XXXX University records. Your breast lump and basal cell carcinoma should not be factors in your decision. I could not determine why you were on acyclovir. If there is a history of genital herpes

Recommendations and Links

it would be important to screen for vaginal/cervical herpes according to current obstetrical guidelines (I no longer perform obstetrics so cannot comment further).

SUMMARY

You appear, from the records, to be an excellent candidate to be a surrogate for your twin sister from a physical and health perspective, with low but not zero attendant medical risks of another pregnancy. I have attached data documenting why I believe this to be so.

The fibroid appears to be an issue that needs to be managed, but additional MRI information would likely help confirm whether or not surgery is necessary and how this should be approached. Surgery, if the indication is confirmed by MRI or if the sonohysterogram original images are of sufficient quality to be certain of the fibroid's location, should be possible at very low risk and with success hysteroscopically by an experienced surgeon. XXXX University has such surgeons. I have attached ASRM Practice Guidelines that outline the medical facts and recommendations with which mine are consistent.

Many factors have to be considered before agreeing to be a surrogate. I have included information regarding ethical, familial, legal, psychological, societal, financial and other factors that must be considered. In the final analysis, only the patient and her husband can decide whether or not they should proceed. I believe the patient's age and the fibroid are lesser considerations than the greater issues that change life-long relationships in a family.

From a personal perspective as a reproductive endocrinologist who has been privileged to help many patients in this situation, being a surrogate is an incredible gift of life to a twin sister. But because it is such a profound gift, it must be done after careful thought and preparation.

I hope this information is helpful to you in your decision and wish you and your family much success and happiness with your decision.

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GRAND ROUNDS SAMPLE OPINION

Condition 6: Leukemia

Names and details have been changed to protect patient privacy.

EXPERT OPINION PROVIDED BY:

Dr. Charalambos (Babis) Andreadis

Assistant Clinical Professor of Medicine
University of California, San Francisco

ABOUT DR. ANDREADIS

Dr. Babis Andreadis is a blood disorder specialist at UCSF with an emphasis on adult bone marrow transplants and the treatment of Hodgkin's and non-Hodgkin's lymphoma, leukemia, and multiple myeloma. Dr. Andreadis has written extensively on the clinical and genetic determinants of response to therapy and toxicity and patient outcomes in each of these blood disorders. He earned a master's degree in clinical epidemiology, focusing on pharmacogenetics at the University of Pennsylvania. Dr. Andreadis currently also serves as a member of the UCSF Helen Diller Family Comprehensive Cancer Center.

EDUCATION

Medical School Columbia University

Residency New York-Presbyterian Hospital

Cardiology Fellowship Hospital of the University of Pennsylvania

AWARDS

Board Certification in Hematology

Board Certification in Medical Oncology

Board Certification in Internal Medicine

SELECTED PUBLICATIONS

David versus goliath: decision analysis predicts results of a large clinical trial in follicular lymphoma. J Clin Oncol. 2013 Oct 1; 31(28):3608-9.

A Phase I Study of Targeted, Dose-Escalated Intravenous Busulfan in Combination With Etoposide as Myeloablative Therapy for Autologous Stem Cell Transplantation in Acute Myeloid Leukemia. Clin Lymphoma Myeloma Leuk. 2015 Feb 14.

Impact of polymorphisms in drug pathway genes on disease-free survival in adults with acute myeloid leukemia. J Hum Genet. 2013 Jun;58(6):353-61.

SUMMARY FOR THE PATIENT

Thank you for allowing me to review your case and provide my opinion. Before I respond to your questions and provide my recommendations, let me summarize your medical history based on what I have learned from your medical records and the questionnaire you have completed.

You are 43 years old and were recently diagnosed with acute myeloid leukemia (AML). You were initially seen by your primary care physician in August of this year because you were feeling fatigued and having fevers. Blood tests done at that time were concerning for leukemia, so a bone marrow biopsy was performed and confirmed the diagnosis.

You were admitted to the hospital for induction chemotherapy (initial chemotherapy treatment) with two different medications, cytarabine and daunorubicin. Repeat bone marrow biopsies were performed approximately two weeks (day #15) and three weeks (day #21) after you started treatment in order to assess your response. The day #15 biopsy suggested that the chemotherapy was working appropriately, and you subsequently began the next stage of chemotherapy called consolidation chemotherapy. You have also initiated a consultation for a bone marrow transplant.

You are seeking an expert opinion to identify the best treatment plan for your diagnosis of AML. You are interested in learning more about the appropriate timing of your treatment (when you should receive chemotherapy) and would like to know if there are any other treatments you should consider.

I'd like to start by acknowledging how frightening a cancer diagnosis can be and say that your concerns about your cancer care are completely understandable. You have several important things working in your favor, including the fact that your care so far has been excellent.

PATIENT'S QUESTIONS

Before I respond to your specific questions, I'd also like to briefly discuss acute myeloid leukemia (AML). Although you are probably already very familiar with the topic, I think the information will provide a useful framework for my recommendations. Adult acute myeloid leukemia (AML) is a cancer of the bone marrow and blood; in some cases, it can also spread to involve other parts of the body, including the liver, spleen and brain. AML affects a group of blood cells called myeloid cells. Normally, myeloid cells develop into red blood cells (blood cells that transport oxygen in the body), white blood cells (blood cells that help fight infection) and platelets (blood cells that aid in clotting). In AML, however, myeloid cells grow too quickly, accumulating in the bone marrow and spilling over into the bloodstream. As these 'leukemia cells' build up in the bone marrow and blood, they crowd out healthy blood cells, leading to a host of problems, including anemia (low number of red blood cells) and infections.

Is the treatment I am currently receiving the best option for my AML?

I believe you are getting the best treatment for your disease. Let me explain why by talking a little bit more about your AML and the course of treatment you have received so far. Although all patients with AML are often grouped together (because their disease shares some common features when their bone marrow and blood cells are looked at under the microscope), AML is actually a diverse group of disorders that differ at the molecular level. Even though there are patients who have poor outcomes with AML, there are also patients who do really well. In the modern era, we believe the distinct molecular features of AML—and not just the diagnosis of AML—will determine how you will do clinically.

Based on my review of your records, you have favorable molecular features. You have normal chromosomes on your baseline test, and at the molecular level, you were found to have an NPM1 mutation without a FLT3 mutation. While I know this may sound complicated, the bottom line is that this combination of factors is considered favorable. In large patient groups enrolled in clinical trials, patients with the same profile as you had a 60-70% chance of long-term remission, or cure.

After beginning your induction chemotherapy (the first chemotherapy treatment), the biopsy that was done on day #15 showed that your marrow was appropriately empty due to the chemotherapy that you had received. (The goal of induction chemotherapy is to eliminate as many leukemia cells as possible.) This is a good sign and means that no further chemotherapy was indicated at that time. Once we achieve a favorable day #15 marrow, as was the case with you, we wait until your blood cell counts recover (until your bone marrow is adequately producing blood cells) before repeating a biopsy to show that you are in remission. This can take anywhere from 1 to 3 weeks. A bone marrow biopsy done at that time showing remission is an excellent prognostic marker.

Based on the available medical records, it is not clear to me why a bone marrow biopsy was done on day #21 and exactly how to interpret it. It is not routine to do a day #21 biopsy. However I am sure your doctor had good reason to do it. The way I interpret your day #21 biopsy is that you were on your way to achieving remission.

Your blood counts recovered soon thereafter, and you began your next stage of chemotherapy called consolidation chemotherapy. Consolidation therapy is intended to destroy any remaining leukemia cells; chemotherapy is typically given at very high doses over about five days. Unfortunately, this was complicated by pancytopenia (all of the blood cells your marrow produces were low due to the chemotherapy). The intended regimen was high-dose cytarabine (HiDAC) at a dose of 3,000 mg/m2; I believe you received 6,000 mg twice a day on days 1, 3 and 5. (Although your records state you received 600 mg, not 6000, I assume this is a typographical error.) You should continue to receive the HiDAC consolidation therapy for a total of 3 to 4 cycles.

Can you please explain a bit about the genetic testing that has been done and what it suggests about my risk of developing polyps and/or colon cancer in the future? Am I at increased risk?

We generally repeat cycles of consolidation chemotherapy at the time of count recovery (when your blood counts recover)--this means a neutrophil (a type of white blood cell) count over 1,500 cells/uL, hemoglobin (a protein in red blood cells; low hemoglobin levels indicate a low red blood count) over 9 gm/dL and platelets close to 100,000/uL. Count recovery generally occurs anywhere from 4 to 6 weeks following the beginning of the previous cycle. Sometimes treatment may be delayed if patients develop complications from treatment, such as serious infections. Most patients complete this treatment within 6 months.

Are there any other treatments that can help cure me of AML?

Recent reports suggest that additional molecular testing may help better estimate your cure rate. Specifically this would involve testing for mutations (abnormalities) in the IDH1/IDH2 genes; the testing would be performed on your original bone marrow specimen. If you carry these mutations, your chance of a cure is approximately 80%, and there is really no other treatment that comes close to the chemotherapy you are getting in terms of success. If you do not have these mutations, than the chance of cure is a little lower than 70% but still very high.

For patients who are less likely to respond to chemotherapy, a stem cell transplant can improve their outcome. This usually refers to an allogeneic (from another person) stem cell transplant performed using a donor's blood or marrow. The donor can be a matched sibling or an unrelated donor matched through the bone marrow registry. There are also so called "alternative donors", but those would not be a

consideration in your case. Generally, a transplant involves some combination of chemotherapy and/or radiation followed by infusion of the donor's blood or marrow. After the stem cells are infused and enter the bloodstream, they travel to the bone marrow where they begin to produce healthy, new blood cells. Patients can leave the hospital when their blood counts recover, but they must be closely monitored for the next 6 to 12 months to ensure proper engraftment (the body has properly incorporated the donor cells) and recovery of their immune system. Risks from stem cell transplant include graft-versus-host disease (where the new immune system attacks certain organs), infections, and chemotherapy toxicity. Approximately 10 to 15% of patients who undergo this procedure die due to treatment complications.

As you can see, accounting for the toxicities involved, transplant is not recommended for patients like you with a favorable prognosis. We would consider it in your case if there is evidence of persistent leukemia on a repeat bone marrow biopsy now or if the AML was to come back in the future. Transplantation is an option that can be used later down the line if you relapse.

Best of luck to you, in what is no doubt, a very challenging time. I hope this opinion provides you some with useful information and reassurance that you are getting the best treatment available.

RECOMMENDATIONS FOR THE PATIENT

Thank you, XXXXX, for allowing me to participate in your care. In summary:

- *Continue with your current treatment plan.*
- *Undergo a repeat bone marrow biopsy when your counts have recovered from this round of chemotherapy. The biopsy will determine if you are in remission and will be important in planning your future treatment.*
- *Perform molecular assays on your original bone marrow biopsy for IDH1 and IDH2 mutations.*
- *Schedule a consultation at a transplant center so that they are familiar with your case. Based on the information I have, I would not advocate a transplant right now if you are indeed in remission.*

REFERENCES FOR THE PATIENT

Leukemia and Lymphoma Society:

http://www.lls.org/

American Cancer Society:

http://www.cancer.org/cancer/leukemia-acutemyeloidaml/detailedguide/leukemia-acute-myeloid-myelogeno...

REFERENCES FOR THE TREATING PHYSICIAN

Patel JP, Gonen M, Figueroa ME, et al. Prognostic Relevance of Integrated Genetic Profiling in Acute Myeloid Leukemia. N Engl J Med; 366:1079-1089, 2012.

http://www.nejm.org/doi/full/10.1056/NEJMoa1112304

National Comprehensive Cancer Network AML treatment guidelines

http://www.nccn.org/professionals/physician_gls/f_guidelines.asp