Research Explores Link Between Thrombocytosis and Cancer

By Kathryn L. Hale

High platelet counts can be an early indicator of cancer. In fact, about one-third of women with ovarian cancer have an abnormally high platelet count at the time of diagnosis. This paraneoplastic thrombocytosis is also seen in patients with cancers of the gastrointestinal tract, lung, or breast.

While this syndrome has been recognized for many years, its cause, its relationship to the cancer, and its clinical implications—beyond the dangers of blood clots—are unknown.

“We’ve known for a long time that cancer patients are at higher-than-normal risk of developing blood clots,” said Anil K. Sood, M.D., a professor in the Department of Gynecologic Oncology and Reproductive Medicine at The University of Texas MD Anderson Cancer Center. In the 1860s, the French physician Armand Trousseau observed that patients with cancer were more likely than the general population to have blood clots. This phenomenon came to be known as the Trousseau syndrome or Trousseau sign of malignancy: an

Paraneoplastic thrombocytosis in ovarian cancer appears to be mediated by a pathway in which interleukin-6 (IL-6) produced by the tumor stimulates thrombopoietin (TPO) production by the liver, which stimulates overproduction of megakaryocytes and platelets by the bone marrow, leading to thrombocytosis.
unexplained blood clot was a clue to the possible presence of undiagnosed cancer.

Ironically, soon after reporting this sign, Trousseau developed a blood clot in his arm and was later diagnosed with gastric cancer. Dr. Sood saw a similar case firsthand as a medical student, when a mentor’s sudden collapse with a pulmonary embolus was the primary presentation of metastatic colorectal cancer.

A handful of studies have shown that, of people identified randomly as having an unexplained high platelet count, about 40% will have cancer. “A platelet count higher than 450,000/mL is significant and should raise a red flag for the presence of cancer,” Dr. Sood said.

High platelet counts and blood clots have causes other than cancer, of course. Inflammatory, infectious, and autoimmune conditions typically raise platelet counts substantially, as does iron-deficiency anemia. These conditions should be ruled out in any patient with a persistently high platelet count. “We see this thrombocytosis very consistently in a proportion of cancer patients,” said Dr. Sood, “but we have never known why or what it means. Healthy people have to make about 100 billion platelets every day just to maintain homeostasis. In a person with cancer, that machinery is revved up 5–10 times the normal level. We asked ourselves: how does this come about, and how can we control it? And what implications does it have for diagnosis and perhaps therapy?”

Searching for answers

Dr. Sood and his colleagues in the Departments of Cancer Biology, Experimental Therapeutics, Gynecologic Oncology and Reproductive Medicine, Hematology and Oncology, Pathology, Benign Hematology, Biostatistics, and Leukemia at MD Anderson—along with collaborators from various centers in the United States and the United Kingdom—are working to understand thrombocytosis in patients with ovarian and other cancers. Results of their studies were published in the New England Journal of Medicine in February 2012.

Because they had observed that, among women with ovarian cancer, patients with high platelet counts tended to have worse outcomes, Dr. Sood and his colleagues began their research by reviewing the clinical records of patients treated for primary epithelial ovarian cancer.

“We found that patients with thrombocytosis had more advanced disease, a higher rate of thromboembolic complications, and higher levels of CA-125 (a blood marker of ovarian cancer) than did patients who had normal platelet counts. Patients with thrombocytosis also had significantly faster disease progression and shorter overall survival,” Dr. Sood said. The researchers did not know whether the high platelet counts were a reflection of the extent of disease or other factors.

After ruling out inflammatory conditions and anemia, the researchers began looking for associations between high platelet counts and other blood factors. They found a direct relationship: the higher the platelet count, the higher the circulating level of interleukin-6.

This finding set off a series of experiments. In a mouse model of ovarian cancer, the mice with cancer had significantly higher platelet counts than mice without cancer. Furthermore, high platelet count correlated directly with tumor size and number of metastases. Reducing interleukin-6 production in these mice, with an antibody or small interfering RNA, restored platelet counts to more normal levels.

While this was an exciting finding, Dr. Sood said, “At that point, we could not connect the dots as to why interleukin-6 would be causing high platelet counts. Interleukin-6 is a cytokine, a signaling molecule involved in the production and growth of various immune modulator cells, but it had no known direct connection to platelets.”

In January 2011, while attending a conference to present these results, Dr. Sood heard a presentation by two researchers from the United Kingdom who were conducting an early-stage clinical trial of an interleukin-6 antibody in women with ovarian cancer. These researchers were studying molecular signaling pathways related to inflammation and were not concerned specifically with thrombocytosis, but Dr. Sood asked whether they would be willing to share their platelet data. The U.K. researchers agreed.

“It was amazing,” recalled Dr. Sood. “Among the patients with a high baseline platelet count, the platelet counts returned to the normal range within 2½ weeks of starting treatment with the interleukin-6 antibody. We got very excited. This direct evidence of a clinical link between interleukin-6 and platelet counts drove us to push very hard to figure out the whole pathway.”

Charting the pathway

Dr. Sood and his colleagues hypothesized that interleukin-6 produced by
the tumor or the host stimulates the production of some other factor that in turn stimulates platelet production. To test this hypothesis, the researchers returned to mouse models. They looked at the spleens and bone marrow, the most important centers of blood cell production and development. In mice with cancer, the spleens had extraordinarily high levels of megakaryocytes, the precursors of platelets.

A study of human tissue confirmed this finding. The researchers found high levels of megakaryocytes in bone marrow specimens from women with ovarian cancer. In blood samples from a larger group of ovarian cancer patients with thrombocytosis, analysis of 10 factors known to promote platelet production identified two factors that were significantly elevated in the patients with thrombocytosis: interleukin-6 and thrombopoietin.

Thrombopoietin is synthesized in the liver, and little is known about the effects of cancer on its production. On the basis of published data indicating that interleukin-6 stimulates thrombopoietin synthesis, the group developed a model to explain high platelet counts in cancer: interleukin-6 produced by the tumor stimulates production of thrombopoietin by the liver, which stimulates overproduction of megakaryocytes and platelets by the bone marrow, leading to thrombocytosis.

While visiting the University of Cincinnati, Dr. Sood met a researcher who had developed a mouse strain that lacked the interleukin-6 receptor in the liver. As hypothesized, these mice failed to develop thrombocytosis when ovarian cancer cells were implanted into them because the interleukin-6 produced by their tumors could not signal the increase in thrombopoietin that stimulates platelet production. “This was proof that interleukin-6 plays a major role in cancer-related thrombocytosis,” said Dr. Sood.

These findings were supported by clinical data from women with ovarian cancer. An analysis of normal liver tissue from patients who had undergone resection of liver metastases showed elevated levels of thrombopoietin. Furthermore, patients who had low plasma levels of interleukin-6 survived significantly longer than those with higher levels.

In addition to exploring how cancer drives thrombocytosis, Dr. Sood and his colleague Vahid Afshar-Kharghan, M.D., an associate professor in the Department of Benign Hematology, have looked at how platelets affect tumors. Their results support published data suggesting that platelets promote tumor progression. In a mouse model of ovarian cancer, reducing platelet levels by 50% with an antiplatelet antibody inhibited tumor growth by 50% and increased apoptosis (programmed tumor cell death) by a factor of four compared with controls. By implicating platelets in tumor growth, this finding closed the loop suggested by the tumor interleukin-6/hepatic thrombopoietin/thrombocytosis pathway. The mechanisms by which platelets promote tumor growth are not fully known, however, and are a focus of ongoing work.

The researchers also found abundant platelets in the ascitic fluid surrounding ovarian tumors in mice, indicating that platelets are active in the tumor microenvironment. Thus, the cancer-platelet interaction is more complex than suggested by early findings. This suggestion in turn implies that there might be more than one approach to treating cancer-related thrombocytosis.

Testing new treatments

One approach to treating thrombocytosis in patients with cancer is to reduce the production of interleukin-6. The interleukin-6 antibody siltuximab, which is being tested by Dr. Sood’s colleagues in the United Kingdom, is one means of doing this. The antibody not only reduces platelet counts in patients but also depletes levels of the growth factors produced by platelets; this finding suggests siltuximab could boost the effectiveness of chemotherapy. In the U.K. trial, the antibody stopped tumor growth in some patients. In a mouse model of ovarian cancer, treatment with paclitaxel and siltuximab reduced tumor growth by over 90% compared with controls, significantly more than either agent alone.

Dr. Sood also mentioned the recent well-publicized findings that people who regularly take aspirin, which disrupts platelet function, have lower rates of cancer and generally less aggressive cancers. While this was initially explained by aspirin’s anti-inflammatory effect, thinking has started to shift to its antiplatelet effect. This is supported by clinical evidence that cancer patients who receive heparin (an anticoagulant that reduces platelet activation) to prevent clots live longer than similar patients not receiving heparin. These antithrombotic agents may have anti-tumor effects that are just starting to be recognized.

It is not clear yet what any of these findings will mean for cancer patients. What is clear is the potential for long-term clinical benefits for cancer patients who develop thrombocytosis. Since publishing the initial results, Dr. Sood has received correspondence from many oncologists applauding his efforts to explain and treat this very common phenomenon. Dr. Sood expects that the work being done in his laboratory and elsewhere on paraneoplastic thrombocytosis will shed light not only on the potentially serious blood clots that frequently accompany cancer but also on the cancer itself.

FOR MORE INFORMATION
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FURTHER READING
Common ophthalmic complications of cancer treatment—which can result from chemotherapy, radiation therapy, surgery, or stem cell transplantation—include ocular surface disease with dry eyes, eyelid disorders, cataracts, inflammation and swelling of ocular tissue, infections, and bleeding. “Some of these conditions are minor in severity and are readily treatable,” said Stella Kim, M.D., an associate professor in the Section of Ophthalmology at The University of Texas MD Anderson Cancer Center, “but unfortunately, we do see devastating blinding conditions, which can result from rapidly progressing ocular infections or from permanent damage to various ocular structures, requiring immediate medical and surgical intervention.”

Even though many ocular complications are transient or reversible, patients experiencing similar symptoms may have more serious disorders. For example, blurred vision may be due to cataract progression, a common side effect of various cancer treatments, or it may represent a severe intraocular infection or even metastatic cancer in the eye. The ambiguous nature of ophthalmic symptoms makes regular eye examinations and clear communication between doctors and patients particularly important.

Despite being widespread, ocular complications of cancer treatment are, Dr. Kim noted, “probably underreported and undertreated.” Indeed, all types of cancer treatments can produce eye problems, although symptoms and the underly- ing conditions causing them will vary.

Certain cancer treatments are more likely to result in ocular complications than others. In general, patients receiving chemotherapy are more susceptible to ocular infections and bleeding as a result of their compromised immune status and their low platelet counts. Patients whose chemotherapy regimens contain steroids are particularly prone to shifting refractive error (requiring a change in corrective lens prescription) due to cataract changes. Many patients experience ocular side effects following stem cell transplantation, especially allogeneic stem cell transplantation. Radiation therapy administered to and near the ocular structures can cause inflammation and continued destruction of all layers of the eye. Head and neck surgery near the eye often causes misalignment of the eyelids and the eye socket that requires surgical intervention. Finally, novel ocular complications have been observed in patients undergoing targeted therapy for cancer.

Cataracts are particularly common in cancer patients who have received steroids. Whether administered as eye drops or systemically as part of a chemotherapy regimen, steroids can induce or accelerate the growth of cataracts. Cataracts may also result from radiation therapy to the eye, brain, or total body.

Cataracts resulting from cancer treatment can be initially managed much like cataracts from other causes. Often, Dr. Kim said, all that is needed to improve the patient’s vision is an updated prescription for glasses. When cataracts cause vision loss that affects the activities of daily living, surgery should be performed to improve the patient’s quality of life. Dr. Kim said, “There are unique surgical considerations related to a patient’s current and previous cancer treatments. As a result, it is always optimal for the surgeon to

**Dr. Stella Kim** performs eye surgery.
Produce Ocular Complications

understand the patient’s cancer history.”

Eye infection also can be a serious problem in cancer patients, according to Dr. Kim. Although often reversible if identified early, infection can cause significant, irreversible damage to all layers of the eye if allowed to progress. Patients undergoing myelo-suppressive treatments are particularly susceptible to all forms of infection. Reactivation of viral infections such as herpes simplex, herpes zoster, or cytomegalovirus is also common in cancer patients, and all these infections can affect the eye in varying degrees. “It’s important for an ophthalmologist to know the patient’s infection history in order to gauge whether someone’s complaint of ‘pink eye’ is from ocular dryness or inflammation or from infection caused by bacteria or viral reactivation.”

Glaucoma, another possible complication of cancer treatment, is most common among patients who have received taxanes, such as paclitaxel or docetaxel. Investigations into the link between docetaxel and glaucoma suggest that the drug may cause endothelial cells to separate from the lining of capillaries in the eye. This separation allows fluid to move from the circulatory system into interstitial spaces in the eye, thereby increasing intraocular pressure. Patients with glaucoma may be treated with medication, surgery, or laser procedures.

For transplant recipients, ocular graft-versus-host disease (GVHD), an increasingly common condition that can affect any part of the eye, is of particular concern. GVHD can be acute or chronic and is especially common after bone marrow and stem cell transplants. In its ocular manifestation, the disease typically involves inflammation of the conjunctiva and tear-producing parts of the eye, leading to pain, dryness, and a gritty sensation. Patients with ocular chronic GVHD are also at increased risk of eye infections. In serious cases, ocular chronic GVHD may result in damage to the cornea and conjunctiva and may even cause permanent loss of vision.

“Patients should be informed that vision fluctuations during chemotherapy can be quite common.”

– Dr. Stella Kim

Kim explained, “A contact lens can serve as a foreign body or as a nidus for an infection on the eye surface. This becomes a greater problem when tear function is very low, as is the case after many forms of chemotherapy and radiation therapy.” Most important, patients should talk to their doctor if they experience any change in vision. Early notification is more likely to allow for intervention while a condition is still reversible.

Physicians can help cancer patients by informing them that they may experience visual disturbances during treatment. “Patients should be informed that vision fluctuations during chemotherapy can be quite common,” Dr. Kim said. “But since symptoms alone cannot predict what type of ocular problems the patient may be experiencing, when in doubt, an ophthalmology evaluation may be helpful to rule out any serious pathology.”

**Research**

Working closely with the stem cell transplantation team at MD Anderson, Dr. Kim is conducting clinical and translational research in ocular GVHD. She will present the results of a study conducted by the International Chronic Ocular GVHD Consensus Group at the annual American Academy of Ophthalmology meeting this November. In addition, Dr. Kim, as the director of clinical research in ophthalmology, oversees the ophthalmology collaboration effort to screen patients for ocular toxicity in more than 60 phase I/II trials from various departments at MD Anderson.

“Our role as ophthalmologists caring for cancer patients is to reassure patients that we will help them through whatever ocular problems their cancer treatments may cause,” Dr. Kim said.

**FOR MORE INFORMATION**

Dr. Stella Kim……………………713-563-0854

www.mdanderson.org/oncolog
New Software May Provide a Standardized Reporting System for Diagnostic Radiologists

By Luanne Jorewicz

Radiologists today still report the results of patient imaging examinations in a manner similar to that which has been used for more than 100 years—by providing narrative descriptions that vary in content and clarity.

In response to this problem, David J. Vining, M.D., a professor in the Department of Diagnostic Radiology and the medical director of the Image Processing and Visualization Laboratory at The University of Texas MD Anderson Cancer Center, has developed a software system, called ViSion, which allows radiologists to create easy-to-use multimedia structured reports.

“We’re an image-centric field,” Dr. Vining said, “and we need to use images to our advantage.” He said ViSion works in a manner similar to Facebook—just as Facebook allows users to tag images with the names of people and events, ViSion enables radiologists to tag key radiology images with anatomy and pathology terms as well as the narrative descriptions dictated by the radiologists. The software then assembles these data into a graphical representation of a patient with the key images linked to anatomical sites.

In addition, according to Dr. Vining, “ViSion’s unique graphical display allows a patient’s entire radiographic history to be viewed in a single image.” The software provides a means to link imaging findings to prior exams in order to generate disease timelines for each site of disease. This allows physicians to watch the progression of disease through changing images while listening to the radiologist’s assessment of each finding. The software also automates the use of Response Evaluation Criteria in Solid Tumors by enabling physicians to generate graphs showing tumor progression or response to therapy.

ViSion’s ability to capture and efficiently manage radiologic information and its use of standardized medical terminology could help physicians reduce errors and make more accurate diagnoses and treatment decisions. Dr. Vining’s software development team has included a feature that enables automatic notification of critical results with return receipt verification, providing a means for radiologists to effectively communicate important results to referring physicians and to track the results of those interactions. Dr. Vining’s team has translated ViSion’s standardized medical terminology into several languages, including Arabic, Portuguese, Spanish, and French, thus enabling the automatic translation of radiology reports.

ViSion interfaces with any image display workstation or picture archiving and communication system that uses a Microsoft operating system, thus making it widely accessible.

Clinical trials are ongoing, and ViSion is scheduled to become commercially available in 2013. Continued development involves expanding the software’s medical lexicon so that ViSion can be applied to other image-based fields (e.g., pathology, endoscopy, dermatology) and creating applications such as data mining and automatic coding for billing purposes.

Dr. Vining’s team is also working on advances such as integrating an eye-tracking system that would monitor the eye movements of radiologists to capture screen locations as they report imaging findings, thus eliminating the need for manual interaction with a computer mouse and keyboard. With features like these, Dr. Vining believes that ViSion can fill the need for standardized radiology structured reporting.

FOR MORE INFORMATION
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Disclosure: Dr. Vining is the founder of VisionSR Inc., a startup company that will pursue the commercialization of the ViSion software.
Smoking-Related Cancers

Cancer risks from tobacco are not limited to the lungs

Most people are aware that smoking is the most common cause of lung cancer, but fewer may know that smoking causes many other types of cancer as well. In fact, according to the Centers for Disease Control and Prevention, cigarette smoking is either the direct cause of or a contributing factor in 30% of all cancer-related deaths in the United States.

Risks to smokers

Of the 250 harmful chemicals in tobacco smoke, at least 69 can cause cancer. For example, smoking may double the risk of one type of skin cancer, squamous cell carcinoma.

Head and neck cancers have long been linked with the use of tobacco, especially in the tissues that inhaled tobacco smoke has to pass through. Smoking is thought to be responsible for 75% of head and neck cancers in women and 45% in men. The rate of oral cancer is 27 times higher in men who smoke than in men who don’t, according to the World Health Organization (WHO). For cancer of the larynx, the WHO states that the risk is 12 times higher for smokers than for people who have never smoked, and alcohol use multiplies this risk.

Tobacco use is also the principal cause of bladder cancer in the Western world, according to the WHO, accounting for 40%–70% of all cases. The WHO estimates that smokers’ risk of bladder cancer is two to three times higher than that of nonsmokers, while the U.S. National Cancer Institute estimates the risk for smokers is four times higher.

Cigarette smoking also increases the risks for acute myeloid leukemia and for cancers of the kidney, pancreas, stomach, uterus, cervix, ovary, and colon/rectum, according to the American Cancer Society.

Other tobacco risks

Exposure to secondhand smoke causes cancer and other diseases and premature death in nonsmoking adults and children. The U.S. Environmental Protection Agency, the U.S. National Toxicology Program, the U.S. Surgeon General, and the International Agency for Research on Cancer have all classified secondhand smoke as a known cancer-causing agent.

Other tobacco products besides cigarettes are also dangerous. While most research has focused on the harm of cigarette smoking, cigar and pipe smoking and the use of smokeless tobacco—such as chewing tobacco and snuff—have also been shown to cause cancer in humans.

Benefits of quitting

Many factors contribute to a smoker’s risk of cancer, including the number of years the person has smoked, the number of cigarettes smoked each day, and the age at which the person began smoking.

The good news is that quitting smoking can significantly decrease a smoker’s chances of developing or dying from cancer. For people who already have cancer, quitting smoking reduces the risks of disease recurrence and of developing a second form of cancer. For cancer patients undergoing surgery, chemotherapy, or other treatments, quitting smoking improves the body’s ability to heal and to respond to therapy. Quitting smoking also lowers these patients’ risk of developing pneumonia or respiratory failure.

Smokers of any age can benefit from quitting smoking. According to the National Cancer Institute, smokers who quit around 30 years of age reduce their chance of dying prematurely from smoking-related diseases by more than 90% compared with people who continue to smoke.

Similarly, those who quit smoking at age 50 years reduce their risk of dying prematurely by 50%. Studies have shown that even people who quit smoking at 60 years or older live longer than those who continue to smoke.

It takes a few years after quitting for ex-smokers’ cancer risk to decline. The benefit increases the longer a person does not smoke. Nevertheless, there are immediate health benefits to quitting smoking, such as improvements in lung function, a lowering of blood pressure and heart rate, improved circulation, and less coughing.

For smokers in almost any age group or health condition, stopping smoking has major health benefits.

FOR MORE INFORMATION

- Talk to your physician
- For information about MD Anderson’s Tobacco Treatment Program, visit www.mdanderson.org/quitnow or call 713-792-QUIT

Photo credit: CDC/Deborah Cartagena

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Biologic Therapies for Rheumatoid Arthritis Not Associated With Increased Cancer Risk

Biologic response modifiers (BRMs) for rheumatoid arthritis are not associated with an increased risk of cancer when compared with traditional rheumatoid arthritis treatments, according to the largest systematic review evaluating such risk in rheumatoid arthritis patients.

Among the BRMs used to treat rheumatoid arthritis are the tumor necrosis factor (TNF) inhibitors adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. BRMs are commonly prescribed as a second-line treatment if the standard disease-modifying antirheumatic drugs fail.

Because several cases of hepatosplenic T cell lymphoma have been reported in children and young adults treated with the drugs, the current U.S. Food and Drug Administration warning labels for all TNF inhibitors note the risk of malignancy. However, data from prior studies of malignancies in patients treated with TNF inhibitors were conflicting.

In the systematic review, researchers used the Cochrane Collaboration database to analyze the results from 29,423 patients in 63 randomized controlled trials of rheumatoid arthritis treatments. As a group, the trials selected compared the safety of BRMs against a placebo or traditional disease-modifying antirheumatic drugs (e.g., methotrexate, hydroxychloroquine, leflunomide) and included only patients who had a minimum of 6 months of follow-up.

The researchers observed no statistically significant increased risk of any type of cancer in patients treated with BRMs compared with the other medications or placebos. In the trials analyzed, 211 patients developed a malignancy. No significant differences existed between patients in the control groups who developed cancer and those treated with BRM therapies.

“Patients are understandably concerned when treatments are linked to cancer risk. These results are reassuring for patients considering biologic therapies for their rheumatoid arthritis,” said senior author Maria E. Suarez-Almazor, M.D., a professor in the Department of General Internal Medicine at The University of Texas MD Anderson Cancer Center. “With this knowledge, clinicians can effectively demonstrate that the benefits of BRMs far outweigh the risk.” The study’s report was published in the September 5 issue of the Journal of the American Medical Association.

IN BRIEF

“These results are reassuring for patients considering biologic therapies for their rheumatoid arthritis.”

– Dr. Maria Suarez-Almazor