Blood test could improve graft-versus-host disease treatment

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University of Michigan researchers have identified the first biomarker of graft-versus-host disease of the skin. The discovery makes possible a simple blood test that should solve a treatment dilemma facing doctors with patients who frequently develop rashes after bone marrow transplants. The biomarker also makes it possible to predict who is at greatest risk of dying of graft-versus-host disease, or GVHD.

GVHD is a serious, frequently fatal complication of allogeneic bone marrow transplants. These transplants, in which a person's own bone marrow cells are replaced with bone marrow cells from a donor, are a common treatment for children and adults with sickle cell anemia, leukemia, lymphoma, myeloma and other blood diseases.

Rashes are very common in patients after bone marrow transplants. They may signal the onset of acute GVHD. But until now, a skin biopsy was the only reliable way for doctors to determine whether the rash is caused by antibiotics commonly used to treat bone marrow transplant patients, or is instead GVHD of the skin, where the disease appears in about half of cases.

Because a firm diagnosis is not easy and the threat of GVHD is grave, many doctors who suspect a rash is due to GVHD prescribe systemic high-dose steroids to suppress GVHD, which further weaken a patient's already compromised immune system.

The U-M scientists identified a key biomarker or signature protein of

GVHD of the skin called elafin. Elafin levels can be measured in a blood test to identify which bone marrow transplant patients with skin rashes actually have GVHD.

The test, which U-M hopes to make available to clinicians soon, will make informed treatment possible, says James Ferrara, M.D., Ruth Heyn Endowed Professor of Pediatrics and Communicable Diseases and director of the bone marrow transplant program at U-M. He is senior author of the study, which appears online this week in *Science Translational Medicine*.

"This blood test can determine the risk a patient may have for further complications, and thus physicians will be able to adjust therapy to the degree of risk, rather than treating every patient in exactly the same way," says Ferrara.

"For example, patients at low risk do not need to have additional medicine to further suppress their immune systems. Or patients with high levels who do not respond rapidly to standard treatment could be treated with additional therapy."

The researchers also found that bone marrow transplant patients with high levels of elafin were more likely to die of GVHD than people with low levels. That information also could guide treatment choices. A method to evaluate treatment options is badly needed because transplant patients today often require more than 20 different medications a day, many with very serious side effects.

"This is a good example of how proteomics, the large-scale study of proteins, can help lead to personalized medicine in the future," says Ferrara.

More than 18,000 people in 2005 had allogeneic bone marrow

transplants or autologous transplants, in which a person's own cells are used. About half of allogeneic transplant patients develop significant GVHD, in which cells from the donor attack and destroy the patient's cells. Affecting the skin, liver, and gastrointestinal tract, GVHD is a serious complication for an otherwise life-saving treatment.

Research details:

"Our work is a good example of research that could translate from the bench to the bedside," says Sophie Paczesny, M.D., Ph.D., a U-M assistant professor in pediatric hematology-oncology and the study's first author. She cites a fruitful collaboration between the U-M team and scientists led by Samir Hanash at the Fred Hutchinson Cancer Research Institute in Seattle, "allowing us to validate the lead candidate into a useful blood test."

Using mass spectrometry, the scientists screened a large number of proteins in the blood and skin of bone marrow transplant patients to search for biomarkers involved in GVHD of the skin. A biomarker is a protein present in blood or other bodily fluids whose level can be measured to determine if a disease is present.

Elafin emerged as a significant biomarker. It is made in the surface layer of skin cells in response to certain inflammatory proteins involved in GVHD.

Using blood samples from bone marrow transplant patients with and without GVHD, the researchers found that people with GVHD overproduced elafin in their epidermis. The researchers then looked at 500 patients with skin rashes, and found high levels of elafin in those with GVHD rashes, but not in people with other rashes.

By tracking people with high and low elafin levels over time, they also

found that those with high levels of elafin died from bone marrow transplant complications three times more often than patients with low levels.

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