

Introduction to Aplastic Anemia and Myelodysplastic Syndromes

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Originally published 2000

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The following is an overview of myelodysplastic syndromes and aplastic anemia, what is similar and what is different about them, and why sometimes we get in to trouble trying to separate the two diseases, and why we even talk about an organization that might consider both diseases. They are diseases of bone marrow failure, disorders in which the bone marrow fails to produce what is supposed to be producing.

Aplastic anemia

When we talk about aplastic anemia we are talking about a disorder in which the bone marrow fails to produce enough of the cells that are needed. I spent quite a few years in Detroit, so I have to put everything in terms of the automobile. Think of the bone marrow as a great big factory that has many assembly lines that put out blood cells, just like an automobile plant has many assembly lines that put out a whole bunch of vehicles. If you think of the bone marrow and the assembly line, there are some similarities between them. On the assembly line of an automobile plant, they bring out a chassis and depending upon what kind of cab they put on it or what kind of a body they put on it, what kind of fenders, what kind of tires, you might get a pickup truck, you might get a five passenger vehicle, it might be a four door sedan, or it might be a two door. The size engine they put in it will determine much of what it can do.

The same thing happens in your bone marrow where you have many, many assembly lines there. They all start off with the same cell, a stem cell. Through a process of division, called maturation, the stem cell gradually grows into two cells, then those two cells become four cells, and eight cells, and as they go along they differentiate. We call it differentiation when they become more and more like in a mature cell. Just like the chassis doesn't look anything like the final vehicle, neither does the original cell, the stem cell, look anything like or be able to do anything like the mature cell does as they go down those assembly lines. Depending upon what kind of influences the cells are under, some will become red blood cells, some will become granulocytes, and some of them will become platelets. Just like vehicles going down the assembly line of a car factory one vehicle might become a pickup; one might be a five-passenger car, with two doors or four doors.

In aplastic anemia something bad seems to happen very, very early on the assembly line. As best we can tell the cells in the beginning of the assembly line are pretty good. The original stem cells seem to be fine. But very early in the process of differentiation something happens. Using the automobile analogy, it's like kicking the chassis off the assembly lines, then it falls into the dirt along the side and is destroyed. In the bone marrow, something happens very early in the course of the development of these cells in patients with aplastic anemia and they tend to be wiped out. Researchers now think a lot of this is autoimmune. It is the body's own immune system that is getting rid of the cells. Whether it is because there is something internally defective in that cell that the body recognizes or whether the body is just mistakenly looking at it and it was perfectly good cell that the immune system destroys, is uncertain. It appears more like an abnormal destruction of normal cells. Whatever the reason, the final result is that very few cells get down the assembly line. However, the very few that get by and come off the end of the line are perfectly fine. The problem appears getting passed the initial stage. Some people produce more and some produce less, but the final result is that there aren't very many of these end stage cells produced. Just like the automobile factory example, if something happens to keep knocking the chassis off the assembly line you're not going to get very many vehicles to come out at the end of the day. It is similar in your bone marrow. If you destroy these cells very early on in their development you are not going to get very many mature cells coming out.

Recent studies seem to indicate that most people with aplastic anemia have at least a fair number if not an almost normal number of the very earliest of those stem cells present in the bone marrow. If that's confirmed and holds up, then that offers a potential for a lot of therapies in the future. The end result of the decreased production of cells is that we develop something called **cytopenias**. Cyto means cell. Penia means few in the blood. Thus it means that you have very few blood cells in the blood.

There are three different types of blood cells. When the number of red blood cells is down you have **anemia**. When the white cells are down you have **granulocytopenia** and when the platelets are down you have **thrombocytopenia**. But the interesting thing about aplastic anemia is that the cells though few in number look normal. The red

cells may be a little on the big side but in general they are normal. The white cells are normal and the platelets are normal. Also, they function normally and many people with aplastic anemia can get along fairly well with the very few cells that they have because they do function so well.

When you go in and look at the factory, or the bone marrow, in aplastic anemia what you find is that the people have an almost empty factory, all the assembly lines are pretty well empty. Most of the bone marrow has been replaced by fat. The bone marrow is described as **hypoplastic**. Aplastic anemia is defined as being a marked cytopenia, the absence of cells in the peripheral blood and the presence of a hypoplastic bone marrow, very little bone marrow functioning. Finally, in aplastic anemia there is no evidence of any abnormality in the cells that are produced. They are normal appearing cells; there is no dysplasia.

We usually try to look at the chromosomes in the cells. The chromosomes in the cells are the computer center that drives the cell, telling the cell what to do and how to do it. They tell the cells when to divide, when not to divide. They tell the cells how to differentiate. The nucleus of the cell contains the chromatin and the chromatin is in the form of chunks, large pieces that we call chromosomes. When we look at the chromosomes under a microscope and study them in patients with aplastic anemia, no abnormalities are seen. The cytogenetics or chromosomes are normal. The cells that are produced they appear normal. The granulocytes have good-looking granules and the platelets have good looking granules and they all function fairly well in the disorder we call aplastic anemia.

Aplastic anemia is divided or classified according to one of two ways or often both ways. There are a group of people who usually develop aplastic anemia early in life who have a predisposing disorder that we recognize and know frequently leads to aplastic anemia. Patients with Fanconi anemia are patients who frequently develop severe aplastic anemia. Other patients with dyskeratosis congenita frequently will develop aplastic anemia as well. We call these cases of aplastic anemia the **inherited form**. The patients are usually not born with the aplastic anemia itself but are born with a predisposition to develop it.

We also have what we call the **acquired form**. These are patients who develop aplastic anemia and we don't recognize any underlying predisposition leading to the disease. There could very well be and sometimes we can identify an unusual factor that may have led to aplastic anemia but in general we

can't readily identify an underlying predisposition and so we call those people acquired. These are the people that we sometimes recognize as having acquired their aplastic anemia from some exposure to chemicals such as benzene.

We also classify aplastic anemia, according to how severe it is. If a patient has a consistently low platelet count below 20,000 per cubic millimeter in the blood, which is about 20 billion platelets per liter of blood (about a quart), sounds like an awful lot but it's really quite low, and if they have a consistently low granulocyte count of less than 500 million (a half a billion per liter), and they have a consistently low reticulocyte count, which means that they are making very few red cells, we call that **severe aplastic anemia**. If the counts are not that bad, then it's less than severe and we call it **moderate or mild aplastic anemia**. We also subcategorize those who are severe into a group who are **super severe** if they have a granulocyte count that is persistently less than about 200 per cubic millimeter (200 million or a fifth of a billion per liter of blood) because those people are very prone to infections. That is what we are talking about when we're talking about degrees of severity of aplastic anemia.

Myelodysplastic Syndromes

MDS on the other hand have several similarities to aplastic anemia. They also are characterized by cytopenias, a marked reduction in the number of red blood cells, frequently in the number of white blood cells, the granulocytes and often in the number of platelets. Different patients with different kinds of MDS will have different degree of cytopenias, but one thing that is common to all of them is anemia. They often have low white and platelet cell counts like the patients with aplastic anemia as well. But there is a difference.

Using the comparison of an automobile factory, instead of all of the assembly lines working properly, something happens and one of the assembly lines starts putting a defective chassis on the line and because it does that, the other lines seem to close down and only one of the assembly lines functions and it is working overtime. Soon it is the only assembly line in the factory and it expands so it takes up all the space in the whole factory. All the other assembly lines seem to disappear.

The same thing happens in the bone marrow. Instead of many different cells producing a host of cell lines coming down this differentiation pathways as in a normal bone marrow, it appears that only one stem cell is working and it is defective. All cells

produced in the bone marrow are coming from this one defective cell. However, they are not being destroyed as defective cells as would normally happen. They pile up in the bone marrow so the bone marrow starts looking like it's packed full yet there aren't many normal cells in the peripheral blood.

Recent data seems to indicate that the reason for this is that the body has a normal mechanism that allows a cell that is worn out, used up or defective to recognize it's defect. Then it is programmed to destroy itself. The cell has a built in self-destructive mechanism called **apoptosis**. Apoptosis is the normal way the normal cells in the body tend to die. It appears that the ability for apoptosis is retained by the defective myelodysplastic cells and about the time they are supposed to be released into the bloodstream they tend to destroy themselves so that much of the cytopenia is due to the self-destruction of these cells after they are well along the line of maturation. Thus the end result is that these patients have cytopenias.

Because there is an overproduction of these cells most of these patients, when bone marrow is examined, it will appear **hyperplastic**, having an excessive number of cells. However, in about 15% of these patients who have an obvious dysplastic clone, that is they have evidence that a single clone of cells are being produced which has a defect in that clone and thus are abnormalities in the cells produced, about 15% are going to have a very, very small number of cells in their bone marrow, or **hypoplastic** bone marrow. The number of cells in the marrow will be very decreased. Because the cells that are produced are coming from an abnormal precursor cell they are going to be dysplastic.

Using the auto factory comparison, it is the same thing as if there is something wrong with the basic chassis or motor you are using to make a car. When it comes to the end of the production it may look like a car but it has obvious looking defects and it isn't going to work well because of the defect. So too in MDS patients, the cells that come out of the bone marrow tend not to function as well as normal cells. Unlike the aplastic anemia patients whose few cells are normal and function well, these patients tend to have poor function of the cells produced. They may have far fewer granules in their granulocytes which may not function well, leading to infection. The platelets may appear washed out and pale and not function well, leading to bleeding. The red cells tend to be huge, out of proportion and oddly shaped. The various cells that are produced do not function as well as the normal cells.

As mentioned before, there is good evidence that all of the cells that are in the bone marrow appear to be coming from a single stem cell and so are a "clone". That is why MDS is called a **clonal disorder**. One clone of cells is producing all of the cells in the marrow. There is only one stem cell. All the cells are derived from that one cell.

Myelodysplastic disorders are usually classified according to what is seen in the bone marrow and the peripheral blood. All forms of MDS have severe anemia associated with them and they are frequently called a refractory anemia since it does not respond to the usual treatments for anemia. If there is no other major abnormality such as not a lot of blast cells (immature blasts in the bone marrow and none in the peripheral blood), and if the red blood cells do not show and inability to incorporate iron and make the sideroblasts, then it is called **refractory anemia (RA)**. If when you look in the bone marrow you see that many of the developing red cells have lots of iron in them that has not been made into hemoglobin and it forms a ring of iron containing granules around the nucleus or center of the cell, it is called **ring sideroblast**. If you have a lot of those in the bone marrow, then we call that **refractory anemia with ringed sideroblasts (RARS)**. Both the refractory anemia alone (RA) and the refractory anemia with ringed sideroblasts are separated because those patients in general tend to do much better than the other three groups. Those who have refractory anemia and also an increase of the number of blasts we call **refractory anemia with excess blasts (RAEB)**, providing the percentage of blasts is still less than 20% in the bone marrow. If between 20% and 30% blasts are present in the bone marrow, it is called **refractory anemia with excess blasts in transformation (RAEB-T)**. Then we have a fifth group, called **chronic myelomonocytic leukemia (CMML)** in which there is usually not a significant increase in blasts but there is a great increase in monocytes and a marked anemia. Those patients are put into a category called chronic myelomonocytic leukemia (CMML) and it has an exceedingly variable duration. Some patients do quite well with it, others do very poorly with it. At the present time, these are the five categories used in classifying MDS.

Hematologists try to make prognostic guesses by giving a value to how low platelets, hemoglobin, and granulocytes are and to how increased the number of blasts is. Each factor present is given one point. So if a patient has very low hemoglobin that's one point. If there is a very low granulocyte count its another point. If there is a low platelet count, its

another point. If an increase in blasts is present, there is another point. Points are totaled; the higher the number of points in general, the poorer a patient will do.

Similarities

So we see that the two disorders have many similarities between them. They both present with cytopenias, that is low counts as their major clinical problem and the problem that bothers patients the most. Almost all of aplastic anemia patients and a significant percentage of myelodysplastic patients will also have a very hypoplastic bone marrow. Both disorders do increase with age, that is the number of cases of myelodysplasia and aplastic anemia increases with the age of the population.

One very interesting thing is that many patients show clearly having aplastic anemia will later develop myelodysplastic syndromes. This is much more common in patients who have been treated with immune suppressive agents. It is not known whether that is because of the treatment with immune suppressive agents or because these people have survived much longer because they have responded to the immune suppressive agents. A significant percentage of these patients that go on to develop myelodysplasia. Some of the early studies said as many as 35 to 40% of patients develop MDS. More recent studies seem to indicate a lower number of aplastic anemia patients develop MDS. I wonder if in the earlier days, many of the patients we thought had aplastic anemia had we had better diagnostic tools, we might have called them myelodysplasia too. Certainly aplastic anemia on occasion becomes myelodysplasia. Both of them then can go on to develop leukemia.

Interestingly the treatment for both is very similar in many ways. That is curative therapy with bone marrow transplantation certainly works in both aplastic anemia and myelodysplastic syndromes. There have been reports that patients with the hypoplastic form of myelodysplastic syndromes and certainly the patients with aplastic anemia respond to immune suppressive therapy.

The supportive care of both types of patients is very similar. Both require transfusion therapy -- red cells, and occasionally platelets. A lot of patients are going to need treatment for infections if their white counts are very low.

There is fairly good evidence that there are certain causative agents that can lead to aplastic anemia such as radiation and benzene. We know

that both of those agents can cause myelodysplastic syndromes.

So in many ways they are similar disorders. Both increase incidence with age. Although hematologists see many more younger people with aplastic anemia than with MDS. Doctors are recognizing MDS more often in younger people now, than they did a few years ago.

Differences

There are however, differences between the two. MDS clearly demonstrates a clonal proliferation, a single stem cell producing all the cells in the bone marrow. In aplastic anemia there have been differences in reports as to whether there is clonality of hematopoiesis or not. Some studies have indicated that there may be only one, two or three clones functioning in an aplastic anemia patient, but other studies have not been able to confirm this. They seem to indicate that there are multiple clones still functioning. MDS is definitely a single clone of cells that seems to be functioning.

The aplastic anemia patient produces normal cells - they tend to be normal in appearance and they tend to function well. Blood cells in the myelodysplasia patient tend to be abnormal in appearance and function. There are differences in the bone marrow appearance as well. Patients with myelodysplasia tend to have a marrow that is packed with cells or at least an increased number of cells in the bone marrow. Only a small percentage (about 15%) of MDS patients present with very few cells in the marrow. The opposite is true for aplastic anemia. Nearly all aplastic anemia patients have a very empty looking bone marrow.

Both disorders increase with age, making one think (or at least the epidemiologist tell us) that if you have a disorder such as this that increases with age it probably means that several factors are working to produce it. However, aplastic anemia is certainly seen much more frequent at a lower age than are the cases of myelodysplasia. ◆