Differential Diagnosis of Anemia and Cancer

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Although anemia is a very common manifestation of cancer, it is present in a moderate to severe degree (hemoglobin less than nine gm./100 ml.) in only 20 percent of patients, and then usually in those with advanced disease. Only occasionally will the symptoms of anemia be the presenting complaint of the cancer patient. In general, well-being is influenced by several disease manifestations, and relief from one can often greatly benefit the patient. It is important, therefore, to understand the mechanisms of anemia associated with cancer and to apply appropriate therapeutic measures when possible.

Very few comprehensive articles have been written on this topic, and most describe only a single form of anemia. Relatively recent articles have been written by Ley,2 Hyman and Harvey,3 both in the mid-1950s, and by Kremer and Laszlo in 1973.4 The following article presents an overview of the differential diagnosis and management of 10 causes of anemia that occur with cancer. This includes: anemia of chronic disease; blood loss anemia; aregenerative anemia; leukoerythroblastic anemia; pure red cell aplasia; autoimmune hemolytic anemia; microangiopathic hemolytic anemia; hypersplenism; megaloblastic anemia; and the dyserythropoietic syndromes.

Anemia of Chronic Disease

Anemia of chronic disease is characterized by mild to moderate anemia (hemoglobin usually above nine gm./100 ml.), caused by an increase in red cell destruction and a failure of the bone marrow to compensate with an adequate production.5-7 Normally, this type of anemia manifests with a low reticulocyte index, hypoferrremia, decreased iron binding capacity and low saturation of transferrin. In contrast to serum hypoferrremia, bone marrow iron stores (hemosiderin deposits) are increased. (Table 1.)

The modest degree of shortening of red blood cell (RBC) survival in anemia of chronic disease, as measured by chromium51 labeling, appears to be related to an extra corpuscular factor.8 The defect is undefined but may be secondary to heightened reticuloendothelial (RE) activity with increased destruction of red blood cells.9 Plasma iron turnover rates and red cell iron turnover rates indicate that total and effective erythropoiesis are between one and two times normal in these patients.5,8 It is not known why the bone marrow, which normally can increase its production by six or eight times, does not respond more ade-
quately. Factors that may be responsible include: reduction in the production of erythropoietin stimulating factor (ESF); impaired marrow response to ESF stimulation (marrow cellular defect); and inadequate iron supply for an accelerated rate of erythropoiesis.

Although several investigators have noted that ESF deviations were less than would be expected for the degree of anemia,\textsuperscript{10-12} Douglas and Adamson found that in more than half their patients, ESF fell within the range of comparable anemic controls.\textsuperscript{5} Others, using in vivo\textsuperscript{12} and in vitro\textsuperscript{11} techniques, have shown that the marrow of patients with anemia of chronic disease may not be as responsive to ESF stimulation as that of normal patients.

Hypoferremia associated with anemia of chronic disease may prevent the bone marrow from compensating for red cell destruction; low serum irons would limit marrow erythropoiesis to one-two times normal.\textsuperscript{13} The cause of hypoferremia appears secondary to avid iron uptake by the reticuloendothelial system with decreased outflow.

Unfortunately, anemia caused by a chronic disease, such as cancer, does not respond well to therapy of any kind, unless the underlying disease responds to treatment. Most frequently, a trial of oral or intravenous iron is given. However, if the reticulocyte count does not respond within five to 10 days, or if the hemoglobin does not rise within three weeks, the trial should be abandoned, since it unnecessarily adds to the burden of medications prescribed for cancer patients.

**Blood Loss Anemia**

Blood loss, either chronic or acute, is the most common cause of anemia requiring blood transfusions in the cancer patient. Chronic blood loss produces a classic iron deficiency anemia, in which red cell loss of six to eight ml./day exceeds the iron producing capacity of a normal diet. Characteristics of iron deficiency anemia include decreased plasma iron, increased iron absorption, reticulocytosis, decreased MCV, decreased MCH, decreased MCHC and increased iron binding capacity. However, this picture may
be altered by a superimposed anemia of chronic disease, with its associated decreases in iron binding capacity, reticulocytosis and iron absorption. Demonstration of absent bone marrow hemosiderin stores in iron deficiency anemia may be necessary to make the distinction.

In blood loss anemia, the first consideration naturally turns to gross bleeding, but incipient loss should not be forgotten. Bleeding from superficial lesions, especially recurrent breast cancer, can over a period of time become severe enough to cause anemia. Often, it is accompanied by a secondary infection. Bleeding combined with the malodor of infection may have a deep psychological effect on the patient. We advise application of a yogurt dressing, an approach that sometimes leads to a change in bacterial flora and disappearance of the odor.

Colorectal carcinoma, primarily the clinically silent lesion of the right colon, is a well known cause of anemia. Unfortunately, all too often, rectal bleeding is attributed to hemorrhoids, without proper examination. In older persons, rectal and sigmoid cancer lead to straining and the concomitant worsening of hemorrhoids, adding a further element of diagnostic confusion.

Hematuria is a common symptom of renal cancer. Since it may result from congestion or invasion of vessels close to the tumor, bleeding does not always indicate spread to the renal pelvis. It is usually painless, although blood clots can cause severe spasmodic pain as they pass through the ureter. The hematuria may wax and wane, causing a false sense of security.

Also dangerous, because it is so often attributed to benign factors, is vaginal bleeding, which is the most common early sign of endometrial or cervical cancer. The vast majority of these cancers occur in postmenopausal patients, and bleeding must be cause for immediate alarm and action. According to Taylor and Millen, about 60 percent of vaginal bleeding in postmenopausal women is due to cancer.14

Other causes of iron deficiency anemia in the cancer patient include: erosions and ulcerations of the gastric and intestinal mucosa induced by stress or drugs (steroid, ASA, indocin); bleeding secondary to thrombocytopenia (drugs, marrow replacement, DIC); and intravascular hemolysis.

Occasionally, it is necessary to quickly replace the lost blood volume with transfusions, especially after acute loss in the older patient. However, in those with inoperable or advanced carcinoma, administration of intravenous or oral iron salts is usually sufficient.

A Regenerative Anemia Secondary to Therapy

A regenerative anemic states are characterized by bone marrow hypoplasia of the erythroid and, commonly, other cell lines. As a general rule, destruction of cell line precursors past the stem cell stage is associated with a rapid decrease of precursors and mature cells, and an equally rapid recovery as the stem cells and other early precursors divide and repopulate the marrow.

 Destruction of stem cells is associated with a slow fall of mature cells and a delayed recovery. Permanent hypoplasia may result from repeated destruction of stem cells or destruction of a large proportion of them.

Most chemotherapeutic agents are active against rapidly dividing cells. Since stem cells contain only a small proportion of dividing cells, they are not seriously affected by most agents. The alkylating agents are important exceptions, for they act on the stem cell compartment as well as destroying later precursors. The nitrosoureas seem to have a selective action on the stem cells. In addition, cancer patients often ingest drugs other than chemotherapeutic
agents that are capable of causing aplastic anemia. (Table 2.) The pathogenesis of this type of anemia is not well delineated, but may be associated with an immunologic factor. Of course, radiation destroys cells at all levels of development, including stem cells.

All of these subcategories of regenerative anemia are characterized by a decrease in red cell mass, normal indices, reticulocytopenia and a hypoplastic marrow. During recovery, the marrow may be hyperplastic and/or megaloblastic, while peripheral counts are still low. Ferrokinetic studies show markedly decreased red cell iron utilization and a decreased plasma iron turnover.

Chemotherapy
One of the most frequent errors in clinical oncology is the unjust attribution of an anemic state to an antitumor agent. Many courses of vincristine and bleomycin have been withheld because of "low counts." Similarly, very low hemoglobins have been nonchalantly attributed to cyclophosphamide when the white count and platelet count were normal. Physicians using these drugs must know which agents do and don't cause hematologic depression, which elements are affected and when the nadirs can be expected to occur.

As stated earlier, most chemotherapeutic agents act on rapidly dividing cells. Those cells that have a long life-span past cell division (red cells, 120 days) often will not decrease in number in the peripheral blood, whereas those with a short life-span past final cell division (platelets and granulocytes), will decrease rapidly. Anemia is often
never seen using pulse chemotherapy, and is rare with many chemotherapeutic agents, unless accompanied by other signs of bone marrow depression, such as leukopenia and thrombocytopenia. Notable exceptions to this rule are the alkylating agents and nitrosoureas, which may cause anemia even in the absence of leukopenia and thrombocytopenia. Bleomycin and vincristine do not cause significant hematologic toxicity in most currently used regimens. Obviously, if the drugs are administered on a daily basis or if large, intermittent doses are given before recovery is complete, a different pattern may result. Permanent aplasia is rarely seen with adequately applied chemotherapy, and even the most severe myelosuppression usually rapidly recovers.

Guidelines on when various cancer chemotherapeutic agents have their maximum effect on the peripheral blood count and on the approximate time to recovery are listed in Table 3. However, today, most drugs are used in combination, and it is no longer feasible to give specific recommendations.

Radiation Therapy

After radiation, depression of all bone marrow elements occurs. Its degree and the time to recovery depend on dose and percent of total bone marrow in the radiated field, as well as the time-period over which the radiation was given. The level of 3000 rads given in fractions of 1000 rads per week was considered the tolerable dose beyond which bone marrow regeneration does not occur. However, doses as low as 2500 rads may cause persistent depression of bone marrow in the irradiated site.16

Total nodal irradiation for Hodgkin's disease poses a particular problem, since doses of 4000 rads and higher are routinely given to 60-75 percent of the total marrow space. Rubin has shown that bone marrow regeneration occurred in areas irradiated with 4000-4500 rads, but it was prolonged and totally unrelated to peripheral counts.16 Between six and nine months after irradiation, there was 36 percent complete and partial return of function. At one and two years, there was 50 percent and 85 percent complete and partial return, respectively. Scans at three and four years did not reveal any further recovery beyond the 85 percent level. In contrast, the peripheral counts (mainly white blood cells and platelets), which usually begin to drop by the second week of radiotherapy, are generally back to normal one to two months after radiation. This has been evidenced clinically by poor tolerance to MOPP chemotherapy for one year after total nodal irradiation involving 60 percent of the bone marrow.17 Consequently, if radical radiotherapy encompassing a sizable portion of the marrow and intensive chemotherapy are to be given within one year, it may be advisable to give the chemotherapy first. However, these matters require further study.

Leukoerythroblastic Anemia

Leukoerythroblastosis can be defined as the presence of immature cells of the myeloid series and nucleated red cells in the peripheral blood. When accompanied by a decrease in red cell mass, the condition is termed leukoerythroblastic anemia. Other features in the peripheral smear include tear drop red blood cells and poikilocytosis.

Classically, this picture is thought to be the sine qua non of malignant infiltrative diseases of the marrow. Leukemia, lymphomas, multiple myeloma and carcinoma can be responsible for the disorder. Of the solid tumors, prostate and breast cancers are by far the most common causes. When coexisting with cancer, leukoerythroblastic anemia usually signifies bone marrow metastases. However, in two recent large series, about 40 percent of cases were not associated with cancer.16,19
### Table 3.
Blood Count Nadirs and Recovery Following a Single Dose or Commonly Used Course of Chemotherapeutic Agents

| Class                        | Blood Elements Most Effected | Day of Count Nadir | Day of Recovery |
|------------------------------|------------------------------|--------------------|-----------------|
| **ALKYLATING AGENTS**        |                              |                    |                 |
| Mechlorethamine hydrochloride (Nitrogen mustard) | Pancytopenia. | 14-21             | 28-42           |
| Melphalan (Alkeran)          | Pancytopenia.                | 14-21             | 28-42           |
| Busulfan (Myleran)           | Pancytopenia.                | 14-21             | 28-42           |
| Chlorambucil (Leukeran)      | Pancytopenia.                | 14-21             | 28-42           |
| Cyclophosphamide (Cytoxan)   | Leukopenia.                  | 14-21             | 28-42           |
| **NITROSOUreas**             |                              |                    |                 |
| BCNU (Carmustine)            | Predominately leukopenia and thrombocytopenia; clinical anemia may be severe if drug has been administered > six months. | 21-35             | 42-56           |
| CCNU (Lomustine)             |                              | 21-35             | 42-56           |
| Methyl CCNU (Semustine)      |                              | 21-35             | 42-56           |
| **ANTIMETABOLITES**          |                              |                    |                 |
| Cytarabine (Cytosar)         | Thrombocytopenia and leukopenia. | 7-14 for most agents. | Variable.       |
| Fluorouracil (5-FU)          |                              |                    |                 |
| Methotrexate                 |                              |                    |                 |
| Mercaptopurine (Purinethol)  |                              |                    |                 |
| Hydroxurea (Hydrea)          |                              |                    |                 |
| **VINCA ALKALOIDS**          |                              |                    |                 |
| Vincristine sulfate (Oncovin) | None.                        | 4-10              | 7-21            |
| Vinblastine (Velban)         | Leukopenia.                  | 4-10              | 7-21            |
| **ANTITUMOR ANTIBIOTICS**    |                              |                    |                 |
| Bleomycin sulfate (Blenoxane) | Usually none.                | 14                | 21              |
| Adriamycin (Doxorubicin)     | Leukopenia.                  | 14-21             | 28              |
| Dactinomycin (Cosmegen)      | Thrombocytopenia and leukopenia; occasional anemia. | 14-21             | 28              |
| Mitomycin C (Mutamycin)      | Pancytopenia.                | 28-42             | 42-56           |
| **MISCELLANEOUS**            |                              |                    |                 |
| Procarbazine (Matulane) *    | Leukopenia, thrombocytopenia. | 28                | Variable.       |
| Imidazole carboxamide dimethyltriazino (DIC, DTIC) | Leukopenia, thrombocytopenia. | 21-28            | 28-35           |

*Usually given as a 14-day course.
Many benign conditions can also cause leukoerythroblastosis, some of which may occur in the cancer patient. These include infection, hemolytic anemia, megaloblastic anemia, alcoholism with cirrhosis, hemorrhage, hepatitis and pancreatitis.

A variant of leukoerythroblastic anemia is myelofibrosis and myeloid metaplasia, simulating agnogenic myeloid metaplasia. In this syndrome, beside leukoerythroblastosis, there is evidence of marrow fibrosis, progressive splenomegaly and extramedullary hematopoiesis, especially in the spleen and liver. Although difficult to differentiate from the primary form, in secondary myeloid metaplasia and myelofibrosis platelet counts are often decreased, giant platelets and platelet fragments are uncommon, chromosomal abnormalities are not noted and splenomegaly is rarely massive, in contrast to the primary form. Bone marrow biopsy will usually reveal metastatic carcinoma. Ferrokinetic studies show an increased plasma iron turnover rate, (increased total erythropoiesis), decreased utilization of plasma iron (ineffective erythropoiesis) and increased uptake by the liver and spleen (extramedullary hematopoiesis), as well as normal marrow transit times.

Pure Red Cell Aplasia Secondary to Tumor

Pure red cell aplasia is a condition in which the bone marrow suddenly stops producing red cells. Bone marrow examination reveals an absence of erythroblasts, but usually normal numbers of other marrow elements. This is in contrast to aplastic anemia, in which the marrow is depleted of all hematopoietic elements. Approximately 50 percent of patients have a thymoma and some experience remission when the tumor is removed. A few patients with carcinoma (gastric cancer, squamous or anaplastic carcinoma of the lung, adenocarcinoma from an unknown primary) have been reported with pure red cell aplasia, without a known thymoma or metastases to the bone marrow.

Many patients demonstrate a plasma-inhibiting factor to erythropoiesis. This factor has been found to be an immunoglobulin with complement-dependent cytotoxic antibody activity against erythroblasts. Treatment consists of steroids, splenectomy and immunosuppressive agents, such as cyclophosphamide.

Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia (AHA), characterized by the presence of a positive Coomb's test and evidence of decreased red cell survival, is fairly common in lymphoproliferative disorders; it occurs in 10-20 percent of patients with chronic lymphocytic leukemia, two percent of those with lymphomas and occasionally in those with multiple myeloma and thymoma. On very rare occasions, AHA has been reported in patients with solid tumors. It must be remembered that several drugs commonly used in the treatment of cancer may induce AHA, such as quinidine, phenacetin, thorazine, sulfonamides, cephalothin derivatives, penicillin, L-dopa and methyl dopa.

AHA occurring with cancer can be arbitrarily divided into two major categories: warm antibody (IgG) and cold (usually IgM). The etiologic basis of either group in connection with cancer is not well understood. Immune hemolytic anemias secondary to drugs, collagen disease or neoplasm are usually of the warm antibody type; cold agglutinin syndromes may occur with lymphoproliferative disorders.

In warm antibody (IgG) hemolytic anemia, the onset is usually rapid and the anemia often severe. Symptoms and physical findings include fever, jaundice and hepatosplenomegaly. The periph-
eral smear contains spherocytes and red cell fragments. Reticulocytes are increased, leukocytosis is common and the bone marrow usually shows normoblastic hyperplasia (unless masked by drugs or irradiation). The platelet count is usually normal. When immune thrombocytopenia coexists, the condition is termed Evans syndrome. The IgG direct Coomb’s is always positive and the C₃ Coomb’s (anti-C₃ and patient’s cells) is often positive. Since IgG associated with warm antibody hemolytic anemia does not fix complement efficiently, intravascular hemolysis is not marked. The predominant method of red cell destruction involves sequestration by the reticuloendothelial (RE) system, particularly the spleen.

Treatment of the warm antibody hemolytic anemias, if associated with RE neoplasia, includes steroids, splenectomy and chemotherapy of the underlying disease. When hemolytic anemia occurs with a solid tumor, steroids and splenectomy are only occasionally effective, and the process usually continues unaffected unless the tumor is eradicated by surgery, chemotherapy or radiotherapy.²⁹

In cold agglutinin hemolytic anemia, the antibody is an IgM directed against the I, i antigen system of the red cell. Hemolysis associated with the cold agglutinin syndrome is both intravascular and extravascular. In lymphoproliferative disorders, the cold agglutinin has anti-I specificity and is most often monoclonal. Symptoms of cold agglutinin AHA include: pallor and/or acrocyanosis of the nose, fingers, toes and areas exposed to cold, which disappear on warming; and symptoms referable to a mild to moderate hemolytic anemia, which is not abrupt in onset. Constitutional symptoms of fever or chills are rare.

The peripheral smear is similar to that of warm antibody hemolytic anemia. However, in contrast, there is no leukocytosis, anemia is not severe and reticulocytes are seldom greater than 10 percent. Direct IgG Coomb’s is positive only if done in the cold; however, the direct C₃ Coomb’s is positive at 37° C. Characterization of the cold agglutinin reveals a monoclonal IgM directed against the red cell I antigen.

Therapy of cold agglutinin hemolytic anemia is not as successful as that for warm agglutinin; steroids are not effective and splenectomy is not helpful unless chromium²¹ studies show definite splenic sequestration. Control of the underlying disease is the only beneficial treatment.

The patient’s own cells are much more resistant than donor cells to hemolysis. Therefore, transfusions should be avoided if possible, as should acidosis and cold, which increase hemolysis.

**Microangiopathic Hemolytic Anemia**

Microangiopathic hemolytic anemia is a rare complication of cancer, but has been seen with carcinoma of the breast and stomach and, less so, with cancers of the colon, prostate, lung, cervix and pancreas.³⁰ Many of the gastrointestinal tumors produce mucin, which, it has been postulated, may be thromboplastic.³¹-³³

Characteristics include red cell fragments (schistocytes), poikilocytosis and anisocytosis in the peripheral smear and, in most patients, thrombocytopenia. There are also signs of hemolysis, such as shortened red cell survival, hemoglobinemia, decreased haptoglobin, increased LDH and reticulocytosis. The mechanism of this extracorpuscular hemolytic anemia appears to be an underlying chronic, disseminated intravascular coagulation.

**Hypersplenism**

Hypersplenism may occasionally present independently from other diseases. It is characterized by a peripheral cytopenia, usually pancytopenia, and a
bone marrow that is hyperplastic for precursors of cells that are in short supply in the peripheral blood. The spleen need not be enlarged, and the condition can only be definitively identified if the cytopenia disappears after splenectomy. Thus, most investigators require the triad of cytopenia, hyperplasia and recovery after splenectomy for diagnosis.

**Megaloblastic Anemia**

Megaloblastic anemia is a morphologic entity based on the finding of macrocytic erythrocytes. (MCV is usually greater than 100 µm³ but may be normal in patients with combined iron deficiency.) Hypersegmented neutrophils and, in severe cases, pancytopenia may be present. The bone marrow shows delayed nuclear maturation and nuclear-cytoplasmic disassociation. Iron stores in the bone marrow are usually increased unless there is a concomitant iron deficiency.

There are many causes of megaloblastic anemia in the cancer patient.35 (Table 4.) Probably the most common are chemotherapeutic agents (purine analogs, antifolates, alkylating agents) and irradiation. However, some tumors, particularly multiple myeloma, are associated with folate deficiency.34 This deficiency may also be seen in leukemic patients and those with disseminated solid tumors.36,37 Patients with pernicious anemia have a 10- to 20-fold greater incidence of gastric cancer than normal patients.38

Megaloblastosis is not in itself an indication for treatment with B₁₂ or folate, since often there is no B₁₂ or folate deficiency. Even if folate deficiency is proven, it may be unwise to administer supplements unless anemia is clinically significant, since folate may be advantageous to tumor growth.

**Dyserythropoietic Anemia**

This term is used to define a group of disorders in which there is a discrepancy
between the number of erythroid elements in the bone marrow and in the peripheral blood. Ineffective erythropoiesis can be due to delayed maturation, disordered cell division or defects in the red cells themselves. Whatever the defect, it leads to a high incidence of intramedullary (bone marrow) cell death.

Laboratory characteristics include a
low reticulocyte count, a rapid plasma iron clearance, decreased erythrocyte incorporation, retention of injected radiioiron within the bone marrow and evidence of hemolysis (increased LDH and hyperbilirubinemia). Folate deficiency and hyperuricemia may also occur.

Morphologically, certain features are common to all dyserythropoietic states, namely asynchrony of nuclear-cytoplasmic maturation and variation in nuclear size and shape. Nuclei are often lobulated, double or multiple with fragmentation and intranuclear budding. The dyserythropoietic states associated with chemotherapy and preleukemia are probably most common in patients with cancer.

Summary

Many patients have multiple causes of anemia. These mixed states render the classical guidelines of peripheral smear, indices, reticulocyte counts and levels of serum iron inadequate for diagnosis. Since the patient with cancer is often under chemotherapy and/or radiation therapy, it is important to ascertain whether the anemia is secondary to bone marrow suppression by treatment, bone marrow suppression by tumor or peripheral destruction or loss. Crucial studies are CBC, platelet count and peripheral smear. (Figure.)

Pancytopenia may be caused by drugs, irradiation, marrow infiltration (leukoerythroblastosis), hypersplenism or severe folate or B₁₂ deficiency. If the patient is at the expected time of a chemotherapeutic or radiation nadir, and the peripheral smear is not unusual, then nothing further is indicated and a “wait and watch” policy may be undertaken. If the patient is not at the usual time for chemotherapy or radiation-induced bone marrow depression, bone marrow aspiration and biopsy should be performed. If the marrow is hyperplastic, the anemia may be caused by peripheral destruction (hypersplenism) or dyserythropoiesis. (B₁₂ or folate deficiency should have megaloblastoid features.) If the marrow is hypoplastic and/or dyserythropoietic, the patient is probably experiencing bone marrow depression from chemotherapy, although preleukemia can also evolve from this type of a picture.

The peripheral smear can be of help, but should not be regarded as diagnostic. In leukoerythroblastic anemia secondary to marrow infiltration, metamyelocytes, myelocytes, nucleated red cells and tear drop red blood cells may be seen. In B₁₂ and folate deficiencies, there may be oval macrocytes and hypersegmented polys. An elevation in the reticulocyte count should always point to hemolysis or blood loss, and red cell fragments in the peripheral smear should alert one to hemolysis. If microangiopathic hemolytic anemia is demonstrated, coagulation studies should also be performed.

Iron deficiency anemia is most commonly seen with gastrointestinal, genitourinary and head and neck tumors, while pure red cell aplasia is usually associated with thymoma. Leukoerythroblastic anemia may be found with any tumor metastatic to the bone marrow, but most often the breast, prostate and lung. Warm antibody hemolytic anemia is generally associated with chronic lymphocytic leukemia, Hodgkin’s and non-Hodgkin’s lymphomas and multiple myeloma. Cold agglutinin hemolytic anemia is seen with histiocytic lymphoma (formerly, reticulum cell sarcoma) and Waldenström’s macroglobulinemia. Folate deficiencies producing megaloblastic anemia may occur in multiple myeloma and leukemia. Gastric cancer is more common in patients with pernicious anemia. Microangiopathic hemolytic anemia most often occurs in patients with adenocarcinomas, particularly of the breast, pancreas and mucin-producing tumors of the gastrointestinal tract.
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