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Update on Pure Red Cell Aplasia: Etiology, Diagnosis, and Treatment

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H&O What is the definition of pure red cell aplasia (PRCA)?

RM PRCA is a normochromic, normocytic anemia that is associated with an extremely low reticulocyte count, and with a virtual absence of red cell precursors in the bone marrow. It is defined morphologically by bone marrow examination. PRCA occurs in many different clinical contexts and as an end manifestation of many different processes.

H&O How common is PRCA?

RM It is difficult to get a handle on exactly how common PRCA is, but it is quite rare, with an incidence of perhaps 1 to 2 cases per million per year. Most hematologists will see at least a couple of cases over the course of their career, however. It is important for them to be familiar with PRCA because it can be treated, in some cases very successfully. Because of the success of treatment, I consider PRCA to be more important than its relative infrequency would suggest. In addition, PRCA is a disease that has helped us develop a greater understanding of the biology of red blood cell production.

H&O What are the causes?

RM PRCA may occur as a primary disease, or as a secondary manifestation of another disease. Primary PRCA, which is also known as antibody-mediated PRCA or idiopathic autoimmune PRCA, is caused by an antibody against erythroid progenitors. This form manifests with an absence of erythroid precursors, along with normochromic, normocytic anemia and a very low level of reticulocytes.

Secondary PRCA almost always results from abnormalities of the immune system, and it has numerous causes. For example, it may occur in lymphoproliferative disorders, particularly chronic lymphocytic leukemia (CLL) and clonal T-cell disorders, and in autoimmune disorders, particularly systemic lupus erythematosus. It can occur in infections, especially with B19 parvovirus, which causes PRCA almost exclusively in immunocompromised patients. It has been reported in all the different forms of viral hepatitis. In addition, a case of PRCA associated with COVID-19 was reported in October 2021 by Yamazaki and colleagues. This appears to have resulted from an immune system abnormality induced by COVID. As of December 3, 2021, the Vaccine Adverse Events Reporting System (VAERS) listed 8 instances of PRCA occurring after COVID vaccination—6 cases with Pfizer, 1 case with Moderna, and 1 case with Johnson & Johnson. Of course, the VAERS database is not able to establish causation.

In rare cases, secondary PRCA may be caused by drugs, particularly anti-infective agents and anti-seizure medications. Secondary PRCA can also be associated with tumors, most notably thymomas. Researchers used

to think that thymomas accounted for 50% of cases of PRCA, but it actually accounts for approximately 5% or 10% of cases. In addition, only about 5% to 6% of people with a thymoma also have PRCA. Pregnancy can be associated with PRCA.

In one widely reported instance, anti-erythropoietin antibodies developed in patients with renal failure who had received recombinant erythropoietin, resulting in many cases of PRCA in the 1990s and early 2000s. Most of the cases occurred outside the United States, primarily in Europe. The outbreak ultimately was attributed to an immune reaction facilitated by the material used to make the stoppers for the prefilled syringes of a particular recombinant erythropoietin product. It was hypothesized that the material served as an adjuvant that helped to support antibody induction. Since a change in packaging, this type of immune reaction has become an extremely uncommon event.

H&O How is PRCA diagnosed?

RM Clinicians should suspect PRCA when they have a patient who has anemia and an extremely low reticulocyte count. When I say an extremely low reticulocyte count, I mean a reticulocyte percentage of less than 1%, and frequently less than 0.1%. The absolute reticulocyte count is characteristically less than 10,000/μL. The diagnosis is a morphologic one and requires a bone marrow biopsy that shows the characteristic absence of erythroid precursors, meaning that they account for fewer than 1% of nucleated cells in the bone marrow (Figure). Alternatively, a diagnosis can be based on a percentage of basophilic erythroblasts—which are one of the very earliest erythroid precursors—that is less than 5% of the nucleated cells in the bone marrow. Clinicians should also conduct standard cytogenetic studies on the bone marrow, along with flow cytometry to identify any associated lymphoproliferative disorder or a traditional myelodysplastic syndrome, such as 5q– syndrome.

After the clinician has established that a patient has PRCA, the next step is to conduct T-cell receptor studies on peripheral blood to identify the presence of a clonal T-cell population. Clinicians also should order a myeloid malignancies panel done with peripheral blood because mutations typical of myelodysplastic syndromes and other myeloid malignancies may occur in PRCA; these panels, usually performed via next-generation sequencing (NGS), have become commonplace in practice over the last few years. The presence of such mutations is unlikely to affect the choice of therapy at present, but researchers are currently trying to figure out what they mean. All patients should also be tested for parvovirus with polymerase chain reaction (PCR) because parvovirus

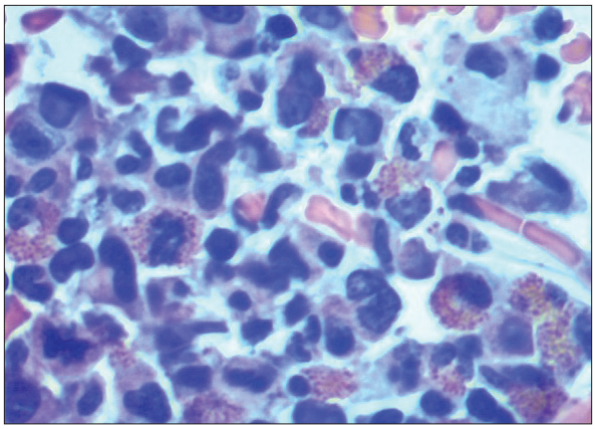

Figure. Bone marrow clot section showing normocellular marrow with near absence of erythroid precursors.

infection requires specific therapy and responds very well to it. Most patients with parvovirus-associated PRCA are severely immunocompromised, so a search for anti-parvovirus antibodies is not going to be a reliable method for detecting parvovirus in their case, whereas the results of PCR testing will be definitive.

Finally, if the patient has PRCA but does not have a parvovirus infection or a PRCA-associated malignancy such as CLL, the clinician should order computed tomography of the chest to see if the patient has a thymoma.

The lactate dehydrogenase level is normal in patients with PRCA unless they have another disorder, such as a lymphoproliferative neoplasm. Although erythropoietin levels are expected to be high in primary PRCA, I rarely measure erythropoietin levels in the evaluation of anemia.

Early recognition of PRCA is important because it allows the clinician to avoid exposing the patient to an excessive number of transfusions, which can lead to iron overload and also carry various immunologic risks.

H&O What treatments are available for PRCA?

RM Although most patients require immunosuppression, the precise treatment of PRCA depends on the cause. If the PRCA is associated with parvovirus, intravenous immunoglobulin will produce a response in more than 90% of cases. Approximately one-third of these patients will have a relapse, but the treatment is simply repeated in such cases.

If the patient has a thymoma, surgery to resect the thymoma is recommended. Resection leads to a response in approximately one-third of cases. The responses to resection are incomplete, however, so people who undergo surgery also require immunosuppression.

Patients with illnesses such as lupus or CLL require appropriate treatment for those diseases. If clinicians

suspect that a patient's PRCA is caused by a medication, they should try switching the patient to another drug, if possible. For PRCA with any other cause, and for primary autoimmune PRCA, the standard treatment is immunosuppression.

At present, the most effective immunosuppressive agent for the treatment of PRCA is cyclosporine, which produces a response in roughly 75% of cases. Corticosteroids such prednisone also are frequently used, sometimes concurrently with cyclosporine and sometimes as first-line therapy before cyclosporine. Corticosteroids on their own will produce a response in probably 40% to 50% of cases. Another option, especially for patients who have PRCA associated with CLL or a lymphoproliferative disorder, is the immunomodulatory agent rituximab. Intravenous immunoglobulin is also commonly used as a third- or fourth-line drug in patients with PRCA who do not have a parvovirus infection.

> In my opinion, the most important current question is, what are the implications of specific clonal mutations for therapy?

Several small studies in patients with treatment-refractory PRCA have revealed promising results with the immunomodulatory drug sirolimus, which appears to be as effective as cyclosporine. Sirolimus seems to be an up-and-coming drug for this disease.

PRCA is unlikely to occur during pregnancy, but if it does, many of the usual drugs are contraindicated. The best option for pregnant patients is usually prednisone or another corticosteroid. If PRCA is caused by pregnancy, it will often resolve after the end of pregnancy. It may or may not recur with future pregnancies.

H&O Is there a role for bone marrow transplantation in PRCA?

RM Successful treatment of refractory PRCA by hematopoietic stem cell transplant has been reported, although only in small numbers. As new immunosuppressive modalities develop, it is hoped that there would be fewer patients in whom that would be a needed option.

H&O What is the prognosis in PRCA?

RM Patients who have a good response to immunosuppression do quite well in terms of survival. Research from Hirokawa and colleagues for the Japan PRCA Collaborative Study Group has shown that median survival in patients with primary autoimmune PRCA who have a good response to immunosuppression is in the 10-, 15-, and even 20-year range. The same goes for patients who have a thymoma or the lymphoproliferative disorder large granular lymphocyte leukemia.

H&O Are any studies of PRCA ongoing?

RM We do not have the opportunity to conduct clinical trials because PRCA is so uncommon. Several large institutions have been able to review their experience with PRCA in a retrospective manner, but conducting a prospective study is difficult. The best recent clinical research has come from the Japan PRCA Collaborative Study Group, which has done multiple studies looking at the course of disease.

H&O What questions need to be addressed?

RM In my opinion, the most important current question is, what are the implications of specific clonal mutations for therapy? Patients with T-cell clonal mutations, which are common in PRCA, appear to respond well to immunosuppression. Are certain clonal mutations, such as myeloid mutations, associated with a reduced likelihood of response to immunosuppression? A consortium such as the Japan PRCA Collaborative Study Group might be able to address this question on a scale sufficient to produce statistically meaningful results.

Another question pertains to patients with a thymoma, who generally receive immunosuppression following surgical resection. That is, what would happen if we skipped surgical resection in these patients and went straight to immunosuppression? I suspect that thymoma resection is still worthwhile, according to the theory that the abnormal thymus is generating the immune dysregulation. However, this has yet to be proved, and we know that two-thirds of the patients who undergo thymoma resection have little or no response.

Disclosure

Dr Means has declared no relevant stock ownership, consultancy, employment, or research support. All drugs in this interview are approved for immunosuppression; none are approved specifically for PRCA. Dr Means has served as an editor of and contributor to chapters/articles on PRCA in Wintrobe's Clinical Hematology, *UpToDate, and* Anemia in the Young and Old.

Suggested Readings

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