“... for the secret of the care of the patient is in caring for the patient.”

—FWP

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Skepticism, the Trained Eye, and the Telltale Clue

Several years ago, I received a call from a colleague. He said, “I need you to provide a supporting opinion concerning my patient. She needs immediate allogeneic bone marrow (stem cell) transplantation as treatment for an aggressive form of myelodysplastic syndrome (MDS). She is a previously healthy 24-year-old woman who developed progressively severe pancytopenia over a 6-month period, and she is dependent on transfusions of red blood cells and platelets. Moreover, we have done two separate, high-quality bone marrow studies, including cytogenetic analysis, and review of these by several hematopathologists and hematologists supports the diagnosis of MDS. We all have advised the patient that this illness could soon be fatal, without an allogeneic-matched donor transplant. We have made an appointment for her at a major facility where the transplantation would be performed. However, she is still frightened by its potential consequences and wants yet another opinion. You need not review the material, because the diagnosis of MDS is well established—just simply convince her of the urgent need for the transplantation and that no other therapeutic approach will be useful.”

I agreed to see the patient. I privately thought that the hematologic diagnosis still might be in error, because the incidence of MDS in a person of her age would be vanishingly low, absent congenital or genetic syndromes. Therefore, I resolved to verify this unusual diagnosis before I complied with the referring physician's request.

I asked for and received the two sets of pathology slides and reports of the bone marrow studies, along with several pages of detailed clinical notes and laboratory data. I found that the patient had no prior history of illness, worked at home as a computer analyst, and was neither ill nor taking any medications when her scattered petechial lesions developed, became diffuse, and were later accompanied by progressive fatigue. Physical examinations and extensive laboratory evaluations had yielded no clues as to possible causes of her illness or potential exposure to toxins. Therapy with corticosteroids and Rho(D) immune globulin had been unsuccessful.

My first conversation with the patient revealed nothing that added to her extensive medical records. My heart sank when I first viewed the slides of her peripheral blood and bone marrow. The blood showed abnormal erythrocyte morphology with macrocytosis, teardrop erythrocytes, and profound neutropenia and thrombocytopenia. There was extreme bone marrow hypercellularity and a nearly total absence of megakaryocytes. Although I noted marked erythroid cellular dyspoiesis and numerous ringed sideroblasts, the few myeloid cells appeared to be normal. Despite the absence of excessive myeloblasts, I suspected that the patient might have an acute erythroleukemia, or what early hematologists referred to as acute Di Guglielmo syndrome. In this illness, the massive, abnormal erythroid precursor population in the bone marrow can obscure visual confirmation of an associated increase in myeloblasts. I had previously observed this phenomenon.

Each of these aberrant morphologic features could be present in any case of MDS. However, the collective findings, particularly the profound thrombocytopenia and absent megakaryocytes, suggested an immune mechanism, but the prior imaging studies had excluded thymoma and splenic pathologic conditions. The more I studied the slides, the more I eerily felt that I had seen this unusual morphologic pattern before—and that it had not been associated with MDS. But where had I seen it? The harder I thought, the more elusive any alternative diagnosis became.

I finally concluded that something important was missing from both my history-taking and the previous clinical notes. I considered what circumstance might be more

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prevalent in a 24-year-old woman than in the older male patient who would more typically have MDS.

I suddenly remembered. In a different clinical situation, I had seen not one, but *two* women who had presented with the same hematologic and pathologic features as this patient. Both women had been in the immediate postpartum period, and their cytopenias had begun in the third trimester. One woman had slowly recovered spontaneously; the other, after short-term corticosteroid therapy. Had my current patient been pregnant? If so, why was this potentially crucial circumstance not mentioned in her medical records?

I returned to the patient (who had not mentioned having any children) and asked her whether she had recently been pregnant. She immediately began sobbing uncontrollably and eventually replied, “I suffered a miscarriage with my first pregnancy, a month or two before my rash appeared. I felt guilty and blamed myself for the loss, and I did not discuss it with my hematologist.”

Her family physician had known about the miscarriage and had mentioned it in passing to the hematologist—however, neither physician had apparently considered it to be relevant to the patient’s current circumstances. Had I not examined the two other women with the same hematologic syndrome, the miscarriage might not have meant anything to me, either. Armed with the new information, I diagnosed a case of immune-related, pregnancy-induced pancytopenia. Because corticosteroid therapy had already failed, I prescribed immunosuppressive therapy with antithymocyte globulin. The patient had completely normal blood counts after a few months.

Full hematologic recovery from pregnancy-induced pancytopenia occasionally occurs spontaneously without specific therapy. However, it typically recurs during subsequent pregnancies, and each successive episode is more severe and more prolonged. I advised the patient not to become pregnant again, but she eventually did, and the hematologic abnormalities recurred during her first trimester. To avoid miscarriage, she took low-dose corticosteroids and cyclosporine, but these provided minimal benefit. Despite manifesting multiple bruises and needing frequent transfusions, she delivered a healthy child at term, with platelet support. Postpartum, after a few months of her taking corticosteroids and mycophenolate mofetil, her blood count returned to normal. A year later, she decided not to tempt fate again and underwent a tubal ligation. Ever since, she and her child have remained healthy with normal blood counts.

The Moral

In the practice of clinical hematology, technical advances in molecular genetics have greatly improved the classification and therapy of certain illnesses but have perhaps diminished the importance of studying classic cell morphology. In addition, physicians should ensure that patients’ medical histories are completely recorded. In this 24-year-old woman’s case, the careful examination of well-prepared slides and the unmasking of a full medical history yielded the accurate diagnosis of an obscure hematologic syndrome.